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GROWTH OF CRYPTS AND GLANDS OF THE HUMAN STOMACH *

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MINNEAPOLIS

I. INTRODUCTION

The prenatal and postnatal changes in the mass and in the capacity of the stomach have been studied in some detail, and the qualitative changes in its musculature are well described. There is, however, almost no information on the quantitative changes in the gastric mucosa in the developmental period, although the applications of such data to gastric physiology in infancy and in childhood are obvious.

The present paper is a report of a quantitative study of one phase of this subject, namely, the growth in number of the gastric crypts and glands in later fetal life, infancy, childhood and adolescence. To this have been added data on the number of these structures in maturity, which were collected as a check on the findings for the developmental period. It is hoped to extend these studies later to a consideration of the dimensional changes of the gastric glands, to the modifications in their finer structure, and to a more detailed consideration of the relations of these findings to various physiologic interpretations of gastric function in the developmental period.

II. MATERIAL AND METHODS

The bulk of the material used in this study was obtained from necropsies of infants and children, which were conducted by the Department of Pathology of the University of Minnesota. The adult material came from the necropsies performed at the University Hospital. In all, forty-five stomachs were examined, but eleven were rejected because of pathologic findings or because of suspicious clinical histories. Table 1 summarizes this material.

The fixation of the material was kept as nearly uniform as possible, Zenker's acetic acid fixative being used in every instance. It sometimes happened that specimens coming from necropsy were temporarily placed in a strong formaldehyd solution, but these stomachs were washed at once and placed in Zenker's solution. The stomachs of the fetuses,

* Received for publication, March 21, 1925.
* From the Department of Anatomy, University of Minnesota.

new-born infants and older infants were fixed in toto. A piece of tissue from 5 to 10 sq. cm. was taken from each adult stomach and fixed in Zenker's fluid. The remainder of the viscus was placed in formaldehyd and later transferred to a 75 per cent. alcohol solution. The material was left in Zenker's fluid for twenty-four hours, washed in running water for twenty-four hours, and then placed in a 75 per cent. alcohol solution; this treatment reduced shrinkage to a minimum. Material to be sectioned was dehydrated, cleared and embedded in paraffin, according to the usual technic.

TABLE 1.—*Summary of Material*

Calculated or Observed Age	Case Number	Sex*	Crown-Heel Length	Sitting Height	Body Weight, in Kg.	Length of Life	Area of Gastric Mucosa in Sq. Cm.	Volume of Stomach in C.c. of Water Displaced
8.11 fetal months.....	19	♀	41	29.3	1.400	0	19.66	3.10
8.16 fetal months.....	11	♀	41.3	27.7	1.255	9 d.	30.58	7.50
8.20 fetal months.....	37	♂	44	31.5	2.205	11 d.	31.58	5.59
8.90 fetal months.....	33	♀	45	31	1.610	0	33.91	5.25
9.04 fetal months.....	24	♂	45.7	32	1.780	0	32.13	4.50
9.10 fetal months.....	34	♀	46	33	2.395	12 h.	31.08	6.25
9.37 fetal months.....	31	♀	47.5	33	2.946	5 h.	33.19	6.55
New-born.....	1	♀	48	31.5	2.900	6 d.	.....	5.50
New-born.....	2	♂	54	38	3.330	0	34.85	13.10
New-born.....	3	♀	50.5	35.5	3.370	0	27.38	7.55
New born.....	4	♂	48	32	3.500	1 d.	35.35	7.55
New-born.....	5	♀	52	36	3.680	0	35.78	4.50
New-born.....	6	♂	49.5	33	3.000	0	41.66	6.00
New-born.....	7	♀	52	34	3.050	0	38.75	11.00
New-born.....	8	♂	52	32	3.400	0	46.91	14.50
New-born.....	9	♂	51	34	3.360	0	45.25	12.10
New-born.....	10	♀	52	34	3.450	0	78.14	15.00
New-born.....	12	♂	54	37.5	3.350	24 h.	39.99	8.10
New-born.....	13	♀	53	36.5	3.230	8 h.	32.51	6.00
New-born.....	15	♂	52	35	2.570	0	39.58	7.00
New-born.....	25	♀	52	35	3.135	9 d.	34.41	16.20
2 months.....	22	♀	49	32.3	3.500	..	113.33	14.60
2 months.....	28	♂	64	43	5.892	..	162.35	21.00
5.5 months.....	21	♂	70	45	5.708	..	159.58	41.00
7 months.....	14	♀	68	46	5.550	..	168.16	25.00
17 months.....	30	♂	82	55	12.000†	..	213.41	42.00
22 months.....	39	♀	87	55	16.000†	..	167.58	40.00
2 years.....	43	♀	88	..	16.000†	..	230.91	44.45
3 years.....	27	♀	92	..	14.000†	..	154.33	46.00
3.5 years.....	32	♀	99	..	16.000†	..	.....	.....
6.5 years.....	29	♂	115	..	.....	..	258.16	85.25
15 years.....	42	♂	139	..	32.000†	..	657.91	247.83
23 years.....	41	♀	160	..	41.000†	..	543.50	230.50
39 years.....	38	♂	171	..	77.000†	..	542.08	234.50
44 years.....	26	♀	...	..	.....	..	470.66	102.75

* In this column, ♀ indicates female; ♂, male.
† Estimated.

The sections for the gland counts were cut at 15 microns, mounted serially, stained in Mallory's connective tissue stain, dehydrated, and cleared and mounted in balsam. Pieces of the stomach with the mucosal surface as nearly flat as was possible to obtain were used in this part of the work. The sections were cut in a plane parallel to the surface of the mucosa, thus presenting the glands in cross section.

Counts of the gastric crypts and glands were made of fifty different areas of 1 sq. mm. for each individual stomach. The counts were made seriatim, aside from the selection necessitated by the irregularities in the surface contour of the gastric mucosa.

The gastric crypts were counted directly from the mucosal surface of the stomach at a magnification of 16 diameters. The crypts were easily discerned under strong oblique illumination. The counts were made with a square representing 1 sq. mm., at a magnification of 16 diameters, ruled off on a coverslip and subdivided into sixteen minor squares. This was placed on the ocular diaphragm of the microscope used in making the counts.

The determination of the surface area of the gastric mucosa presents rather a difficult problem. After trying several methods, the following one was adopted. The stomach was divided in halves by splitting it along the greater and lesser curvatures, and a plaster cast was made of the mucosal surface. Thin tissue paper was then placed on the cast, moistened with water, molded carefully over the surface irregularities and allowed to dry. The tissue paper was then removed from the cast, flattened, and the outlines traced on standard thickness paper which was weighed. Having the total weight of the paper and its known weight per square centimeter, the surface area was easily calculated. This method eliminates the error caused by stretching the stomach in an attempt to reduce it to a flat surface.

III. LITERATURE

The development of the gastric crypts and glands has been a subject of some dispute among embryologists. Kölliker [1] believed the gastric crypts and glands were formed from thickened epithelial processes, which later became hollowed and grew downward into the mesenchyma. Laskowsky [2] thought the fundic glands were formed from invaginated cylindric epithelial cells through changes in their form. Schenk [3] accepts the explanation offered by Laskowsky in its entirety. Wolffhügel [4] gives some information concerning the histologic structure of the fundic glands in older rabbit embryos and in the new-born dog. Brand [5] accepted the views of Laskowsky and Schenk, but considered the connective tissue layer as the causative factor in the process of invagination. He thought that the glands originated from a large number of papillae of mucosal epithelium, which were marked out by the growth of the underlying mesenchyma. In this concept, the part played by the epithelium in the

1. Kölliker, A.: Entwickelungsgeschichte des Menschen und der höheren Thiere, Leipzig, 1861.

2. Laskowsky: Ueber die Entwickelung der Magenwand, Sitzungsb. d. k. Akad. d. Wissensch. Wein. **58**:137, 1868.

3. Schenk: Lehrbuch der vergleichenden Embryologie der Wirbelthiere, Ed. I, Wein, 1874.

4. Wolffhügel, G.: Ueber die Magenschleimhaut neugeborener Saügethiere, Ztschr. f. Biol. **12**:217, 1876.

5. Brand: Beiträge zur Entwickelung der Magen- und Darmwand, Verhandl. d. phys.- med. Gesellsch. zu Würzb. **9**:243, 1877.

origin of the glands is limited to the production of material for the gland cells. Later, Kölliker [6] confirmed and agreed with Brand in this explanation.

Sewall [7] believed the glands were primarily epithelial in origin, but that the chief and parietal cells were later replaced by cells of a mesenchymal origin.

Until Toldt's [8] work, the interest in the development of the gastric glands was limited chiefly to the method of their formation, and comparatively few observations were made on the actual details of their further development. This author, working on cat, pig and human material, decided that the glands and crypts were epithelial in origin and formed by downgrowths of the epithelium.

Johnson [9] described the gastric crypts as originating from vacuoles and pit-like depressions which first appeared in the epithelium on the side of the viscus proximal to the bursa omentalis. These pits increase in number in older embryos and become elongated, rounded or groove-like. The epithelial growth takes place both by the enlargement of the pits already formed and by the addition of new ones. The gastric glands first appear in embryos of 120 mm. as knoblike outgrowths from the bottoms of the crypts. For the most part, these are simple tubular glands, rarely branching, and varying considerably in length and diameter. In the older embryos, the glands become longer and more branched, their growth being more rapid than the growth of the crypts. At birth, the histologic structure is similar to that of the adult. Gundobin,[10] however, states that the glands do not reach the typical adult histologic structure until after the first year.

There is little published information on the number of glands per unit area of gastric mucosa or on the total number of glands in the stomach. Frey [11] estimated as many as 1,894 glands per square millimeter, in the pyloric region of the rabbit's stomach. Sappey [12] counted from 100 to 150 gastric crypts on the smaller papillae (gastric areas) of the mucosa, while the larger papillae gave counts ranging from 600 to 800 crypts, but these observations do not give a concrete expression of

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6. Kölliker, A.: Entwickelungsgeschichte des Menschen und der höheren Thiere, Leipzig, 1879.

7. Sewall: The Development and Regeneration of the Gastric Glandular Epithelium During Fetal Life and After Birth, J. Physiol. **1**:321, 1879.

8. Toldt, C.: Die Entwickelung und Ausbildung der Drüsen des Magens, Sitz. d. k. Akad. der Wissensch. Wein **82**, 1880.

9. Johnson, F. P.: The Development of the Mucous Membrane of the Esophagus, Stomach and Small Intestine in the Human Embryo, Am. J. Anat. **10**:521, 1910.

10. Gundobin, A. P.: Die Besonderheiten des Kindesalters, Berlin, 1912, p. 264, et seq.

11. Frey, H.: Handbuch der Histologie und Histochemie, 1874.

12. Sappey, Ph. C.: Traité d'anatomie descriptive, Ed. 4, Paris, 1889.

crypts per unit area. Sappey considered each crypt a true gland, not as an orifice of a number of glands.

Toldt [8] was the first investigator to determine the number of crypts and glands per unit area of human gastric mucosa. By multiplying this value by the total area of the gastric mucosa, he arrived at an estimate of the total number of glands in the stomach. He hardened the organ by placing it in 80 per cent. alcohol for eight days, then cut it in halves by incisions along the greater and lesser curvatures and spread it flat on a glass plate. The outline was then marked off, and the area calculated with an Amsler planimeter. To count the number of glands, Toldt made permanent preparations cut in such a manner that the glands were seen in cross section. The total number of glands in a given field were counted, and the total number of glands in the stomach were estimated by multiplying the area of the mucosa by the

TABLE 2.—*Toldt's Table*

Age of Person	Area of the Gastric Mucosa in Sq. Mm.	Per Sq. Mm.		Total Number of	
		Gastric Crypts	Gastric Glands	Gastric Crypts	Gastric Glands
Female embryo, end of the eighth (lunar) month (length of body, 39.5 cm.)	2,302	56	404	128,912	930,008
Female embryo, middle of the tenth (lunar) month (length of body, 47.5 cm.)	5,330	50	382	266,500	2,036,060
Stillborn mature male infant (body length, 50 cm.)	5,270	51	371	268,770	1,955,170
Girl, aged 10 years	50,510	56	336	2,828,560	16,971,360
Girl, aged 15 years	65,770	67	341	4,406,590	22,427,570
Man, aged 30	76,300	89	330	6,790,700	25,179,000

average number of glands per square millimeter. The author gives no more details as to his method of counting or as to the number of counts made.

Toldt's table for the increase in number of the gastric crypts and glands is shown in Table 2.

From Table 2 Toldt estimates that the number of gastric crypts increases about fifty-two fold from the ninth fetal month to maturity, while the number of glands only increases in the neighborhood of twenty-seven fold, in the same period. The gastric crypts increase about twenty-five times and the glands twelve times between birth and maturity. In the first ten years the number of crypts increased about eleven fold and the number of glands increased nine fold. According to Toldt's figures, the relation of the crypts to the glands is not changed in the last two months of prenatal life. The average number of glands to each crypt at birth is about seven, in later childhood about six, at fifteen years, five, and in maturity also about five. In the last two months of fetal life the increase in the number of glands is quite large, so that during this period they reach the peak in number per unit area.

After this period, there is no constant relation between the number of gastric crypts and the number of gastric glands.

IV. SUMMARY OF FINDINGS AND COMMENT

The Growth of Gastric Crypts and Glands per Unit Area of the Stomach.—The Gastric Crypts: The gastric crypts (foveolae gastricae) are small pit-like depressions in the mucosa, having at birth an average

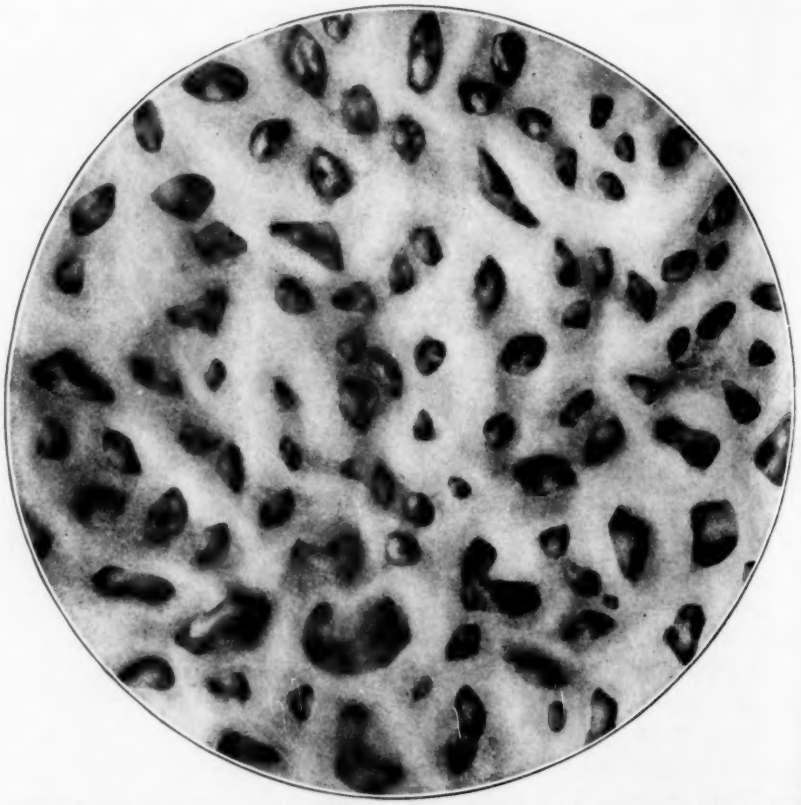

Fig. 1.—A drawing of the surface view of the gastric mucosa of a typical full-term, new-born infant.

depth of 0.108 mm. and an average width of 0.02 to 0.048 mm. (Johnson [9]). At their lower end they receive the openings or mouths of one or more gastric glands (glandulae gastricae propriae). These ostia vary in form, some being elongate, some circular and others groove-like. Their distribution over a given area of gastric mucous membrane is quite constant. When one finds an unusually large crypt, as a rule there are several small ones crowded about it. In the fetuses of the ninth and tenth months they are distinctly larger than in the new-born,

and there is a correspondingly smaller number per square millimeter. Figure 1 is a surface view of a typical area of the new-born gastric mucosa at a magnification of approximately 66 diameters.

Table 3 shows the average number of crypts per square millimeter in fetuses of the ninth and tenth months,[13] as determined by counts on

TABLE 3.—*Number of Crypts in the Stomachs of the Fetuses of the Ninth and Tenth Months*

Number	Calculated Age in Fetal Months	Area of Gastric Mucosa in Sq. Cm.	Average Number of Gastric Crypts per Sq. Mm.	Estimated Total Number of Crypts
19	8.11	19.66	32.14	63,206
11	8.16	30.58	32.08	98,110
37	8.20	31.58	32.46	102,518
33	8.90	33.91	35.48	120,333
Average	8.34	28.96	33.04	96,041
24	9.04	32.13	41.26	132,601
34	9.10	31.08	42.52	132,181
31	9.37	33.19	45.80	152,023
Average	9.17	32.13	43.19	138,935

TABLE 4.—*Range, Interquartile Range and Semi-Interquartile Range Calculated from the Raw Data on the Number of Gastric Crypts Per Square Millimeter*

Number	Age	Average Number of Crypts per Sq. Mm.	Minimum Number	Maximum Number	Total Range	Interquartile Range	Semi-interquartile Range
19	8.11 fetal months	32.14	27	38	11	2	1
11	8.16 fetal months	32.08	27	42	15	2	1
37	8.20 fetal months	32.46	26	38	12	2.5	1.25
33	8.90 fetal months	35.48	30	41	11	1.5	0.75
24	9.04 fetal months	41.26	35	50	15	2	1
34	9.10 fetal months	42.52	36	49	13	2.5	1.25
31	9.37 fetal months	45.80	38	53	15	2.5	1.25
9*	Birth	49.46	40	60	20	2	1
22	2 months	50.21	42	59	17	3	1.5
28	2 months	50.16	40	60	20	3	1.5
21	5.5 months	53.80	48	62	14	2	1
14	7 months	54.06	45	61	16	2	1
30	17 months	64.98	50	75	25	2.5	1.25
39	22 months	67.86	60	82	22	1.5	0.75
43	2 years	65.98	60	73	13	2	1
27	3 years	66.40	58	72	14	2	1
32	3.5 years	66.08	58	74	16	2	1
29	6.5 years	65.60	53	81	28	2	1
42	15 years	61.98	54	77	23	1.5	0.75
41	23 years	60.56	53	70	17	2	1
38	39 years	62.12	57	71	14	2	1
26	44 years	62.84	55	73	18	2.5	1.25

* Case 9 of the new-born series is taken as a typical specimen from this series.

seven specimens. Each average is based on counts of fifty different areas from each stomach. These averages rise from 32.14 crypts per square millimeter at 8.11 months to 35.48 at 8.9 months and 45.80 at 9.37 months. Thus there is an increase of nearly one-half in the number of crypts per unit area between the beginning of the ninth and

13. The estimates of the ages of these specimens were made with the aid of the empirical formula for determining fetal age developed by Scammon and Calkins: Proc. Soc. Exp. Biol. & Med. **20**:353, 1923.

the middle of the tenth lunar month. The most marked increase seems to be in the latter part of the ninth and the early part of the tenth month. The variability of the number of crypts per square millimeter in individual specimens in the fetal period is not very great. It is illustrated by the frequency curves shown in Figure 2 and by the

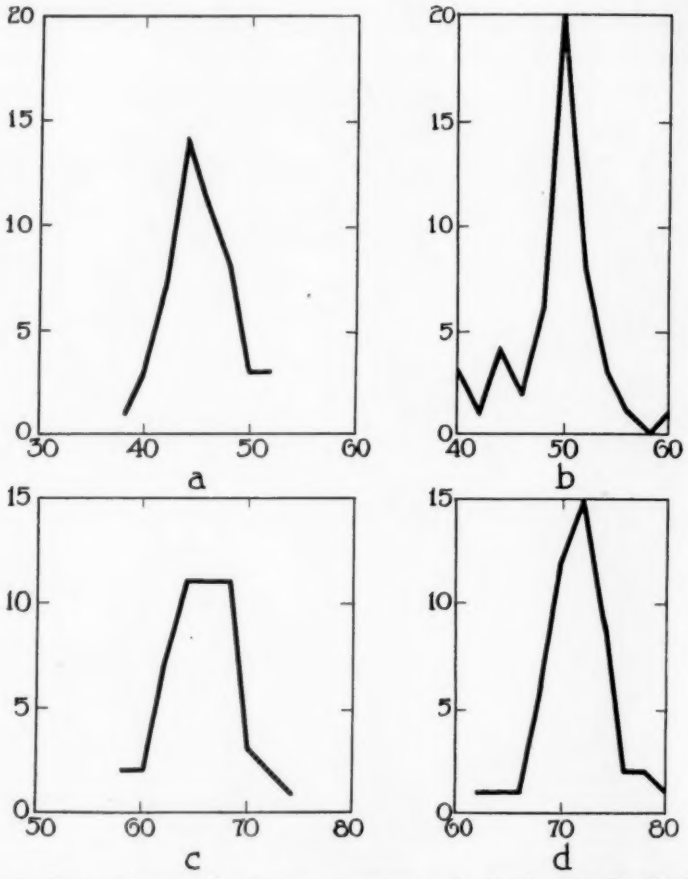

Fig. 2.—Four point-to-point frequency curves each showing the distribution of fifty observations on the number of gastric crypts per square millimeter. Ordinates: number of observations at given values. Abscissas: number of gastric crypts per square millimeter; *a*, fetus of 9.37 months, calculated age; *b*, typical full-term new-born infant; *c*, child aged 3½ years; *d*, adult, aged 23.

values for the total and the semi-interquartile ranges included in Table 4.

The average number of crypts per square millimeter in the full-term new-born infant is 50.24, the probable error of the mean being ± 0.16. The average is based on a total of 700 sq. mm. counts, fifty on each of fourteen specimens. The variability in the number of crypts

per area is somewhat greater than in the fetal material, the standard deviations of the various specimens ranging from 3.95 to 10.82 with an average of 6.08 crypts, and the coefficients of variability ranging from 7.90 to 21.64 with an average of 12.17 per cent. The standard deviation of the entire group of 700 counts is 6.39 crypts, the probable error of the standard deviation being ± 0.16, and the coefficient of variability is 12.78 per cent., the probable error of the coefficient of variability being ± 0.12. Figure 3 is a frequency curve illustrating the distribution of the entire group of 700 counts; Table 5 gives the average count for each specimen with measures of its variability.

The number of crypts per unit area remains fairly constant from birth until some time between the first and the third postnatal months.[14] But between the fifth and sixth months there is evidence of a slight increase in number, the average count at 5½ months being 53.80 per

TABLE 5.—*Range, Standard Deviation, Coefficient of Variability of the Number of Gastric Crypts Per Square Millimeter in the New-Born Infants*

Number	Average	Minimum Number	Maximum Number	Total Range	Standard Deviation	Coefficient of Variability
1	50.70	38	64	26	5.82	11.64
2	50.42	32	82	50	7.67	15.35
3	50.36	38	65	27	5.45	10.89
4	50.06	32	96	64	10.82	21.64
5	50.94	38	82	44	9.70	19.41
6	50.27	39	65	26	6.25	12.50
7	50.76	33	64	31	6.06	12.12
8	49.80	38	63	25	5.33	10.65
9	49.46	40	60	20	3.95	7.90
10	49.54	38	61	23	4.70	9.40
12	49.80	36	59	23	4.72	9.45
13	50.42	40	62	22	5.14	10.29
15	50.18	38	63	25	4.06	8.12
25	50.78	39	71	32	5.51	11.02
Average.....	50.24	..	..	31.3	6.08	12.17

square millimeter. The count is only slightly greater at 7 months but increases approximately one-fifth, to about 65 crypts per square millimeter at 17 months. The average count for the second year is about 66, and it remains almost constant up to 6½ years. No specimens between 6½ and 15 years were available for study. The count at the latter age was approximately 62 crypts per square millimeter; this value, with very slight variations, seems to be typical of the adult stomach.

In summarizing, it may be said that the present data indicate that the number of crypts per unit area of gastric mucosa increases rapidly in the last months of fetal life to birth. It apparently remains constant during the first trimester of postnatal life and then enters on another period of increase which is concluded toward the end of the second year, when the maximum number of crypts per unit area is reached. This

14. One of the two specimens of this period was premature. This factor affected the surface area of the stomach but not the number of crypts per square millimeter.

number remains practically unchanged until middle childhood, but is eventually followed by a slight decrease (the exact date of which is unknown) before adolescence, when the adult number of crypts per unit area is attained.

Tables 6 and 7 and Figure 4 show these changes in more detail. Figure 5 represents a series of camera lucida tracings of 1 sq. mm.

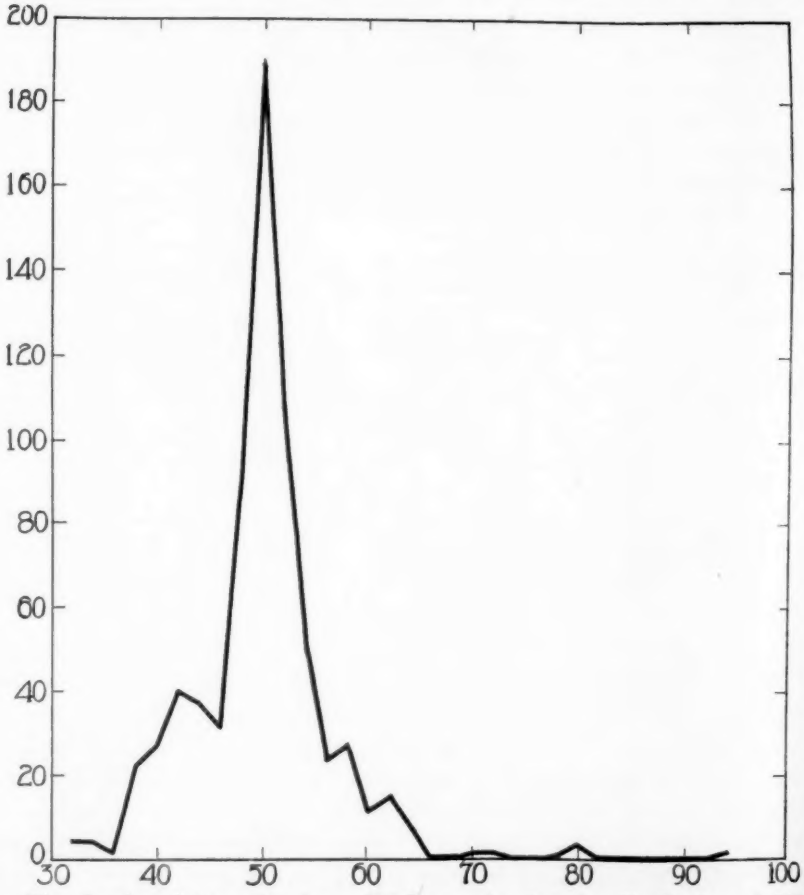

Fig. 3.—A point-to-point frequency curve showing the distribution of 700 observations on the number of gastric crypts per square millimeter in fourteen new-born infants. Ordinates: number of observations at given values. Abscissas: number of gastric crypts per square millimeter.

areas of the gastric mucosa at different ages, drawn at a standard magnification.

The Gastric Glands: The gastric glands (glandulae gastricae propriae) tend to follow the same course of development as do the gastric crypts. In the new-born, they average 0.255 mm. in length and

TABLE 6.—*Number of Crypts in the Stomachs of Fourteen Full-Term New-Born Infants*

Number	Area of Gastric Mucosa in Sq. Cm.	Average Number of Gastric Crypts per Sq. Mm.	Estimated Total Number of Crypts
1*	.....	50.70	.....
2	34.85	50.42	175,713
3	27.38	50.36	137.900
4	35.35	50.06	177,002
5	35.78	50.94	182,278
6	41.66	50.27	209.454
7	38.75	50.76	196,695
8	46.91	49.80	233.641
9	45.25	49.46	223,846
10	78.14	49.54	387,110
12	39.99	49.80	199,155
13	32.51	50.42	163,945
15	39.58	50.18	198,627
25	34.41	50.78	174,764
Average	40.81	50.24	204,625

* The area of the mucosa and the total number of crypts in Case 1 is omitted, as it was impossible to obtain an accurate estimate of the surface area of this stomach.

TABLE 7.—*Number of Crypts in the Stomach in Postnatal Life*

Number	Age	Area of Gastric Mucosa in Sq. Cm.	Average Number of Gastric Crypts per Sq. Mm.	Estimated Total Number of Crypts
22	2 months	113.33	50.21	569,046
28	2 months	162.35	50.16	814,347
Average	2 months	137.84	50.18	691,696
21	5.5 months	159.58	53.80	858,558
14	7 months	168.16	54.06	909,108
Average	6.25 months	163.87	53.96	883,833
30	17 months	213.41	64.98	1,386,781
39	22 months	167.58	67.86	1,137,220
43	2 years	230.91	65.98	1,323,387
Average	21 months	203.97	66.27	1,282,529
27	3 years	154.33	66.40	1,024,773
32*	3.5 years	.....	66.08	.....
Average	3.25 years	154.33	66.24	1,024,773
29	6.5 years	258.16	65.60	1,693,831
Average	6.5 years	258.16	65.60	1,693,831
42	15 years	657.91	61.98	4,077,763
41	23 years	543.50	60.56	3,291,436
38	39 years	542.08	62.12	3,367,421
26	44 years	470.66	62.84	2,957,668
Average	30.25 years	553.54	61.87	3,423,572

* The total number of crypts and the total area of the gastric mucosa in Case 32 is omitted, since only a small piece of this stomach was saved at necropsy.

0.048 mm. in diameter at the neck (Johnson[9]). The accounts given by various workers in regard to the size of the adult glands are quite different. Gegenbaur[15] describes them as being 0.6 mm. in length, partially simple and partially compound in structure. Piersol[16] states that their length is from 0.4 to 2 mm., and that the diameter of the secreting tubule is from 0.002 to 0.007 mm. Testut[17] finds that as many as eight to twelve glands open into a single crypt. Kölliker[18] gives the dimensions as 0.2, 0.75 or even 1 mm. in length and 0.02, 0.26 and 0.036 mm. in diameter. Frey[11] describes the glands as being about 1.13 mm. in length and from 0.0564 to 0.0451 mm. in diameter.

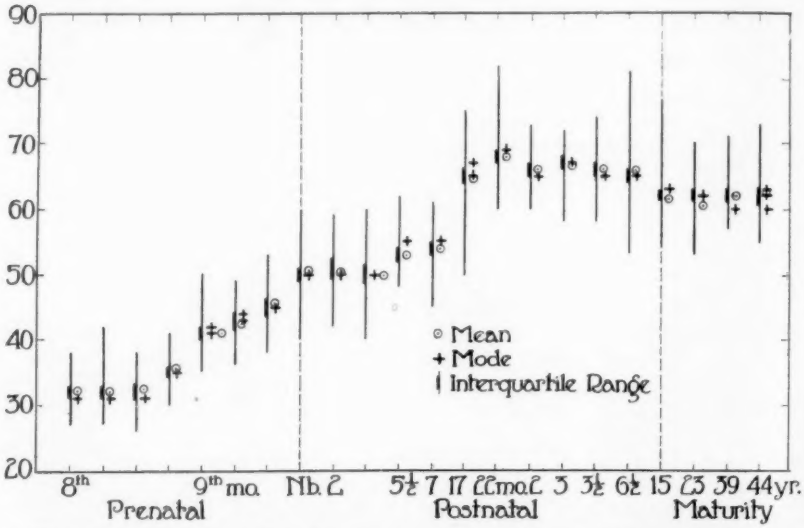

Fig. 4.—A graph showing the range, mean, mode and interquartile range of the entire series of observations on the number of gastric crypts per square millimeter, made in this study. Ordinates: number of gastric crypts per square millimeter. Base line: ages of persons.

According to Frey, the glands are much shorter and of smaller caliber in children. Four, five, six or seven glands may arise from a single crypt.

Table 8 gives the results of the gland counts in the fetuses of the ninth and tenth months; averages for the different ages are derived from fifty counts in each instance. The glands show the same steady increase per unit area evidenced by the crypts for this age. In the fetus of 8.11 months the average number was 77.72 glands per square millimeter

15. Gegenbaur, C.: Lehrbuch der Anatomie des Menschen, Ed. 5, Leipzig **2**:55, 1892.
16. Piersol, G. A.: Human Anatomy, Philadelphia **2**:1621, 1908.
17. Testut, L.: Traité d'anatomie humaine, Paris **4**:133, 1912.
18. Kölliker, A.: Mikroskopische Anatomie **2**:199, 1852.

and the fetus of 8.90 months showed 84.08 glands per square millimeter. The increase is more rapid in the first third of the tenth month than at any other period in the two fetal months studied. In the fetus of 9.04 months the average number of glands per unit area was 92.10 and in the fetus of 9.37 months was 113.36. This corresponds roughly to the rapid increment in the number of gastric crypts per unit area dur-

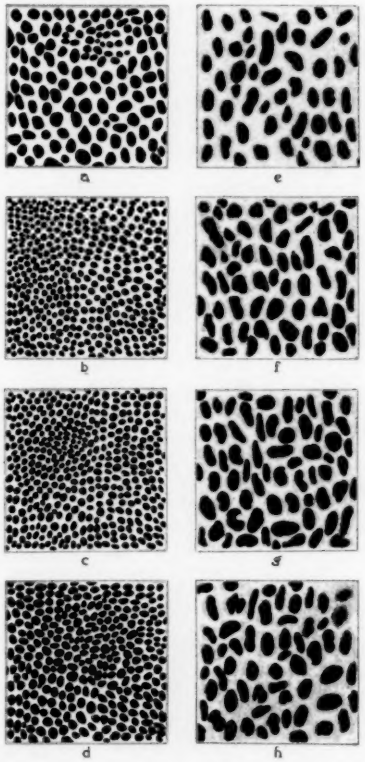

Fig. 5.—*a, b, c, d,* projection drawings of 1 square millimeter areas of frontal sections of gastric mucosa. The black areas represent cross sections of the glands; *e, f, g, h,* camera lucida drawings of 1 square millimeter surfaces of gastric mucosa. The black areas represent the crypts; *a, e,* mucosa of a typical full-term new-born infant; *b, f,* mucosa at 2 years; *c, g,* mucosa at 6½ years; *d, h,* mucosa at maturity. Magnification, 47 diameters.

ing this period. The variation in the range of the observations from which these averages were calculated is illustrated in Table 10 and Figure 6.

In the new-born infant, the number of glands is practically the same in relation to the number of crypts as in the ninth and tenth fetal months. In the 700 areas counted in the fourteen stomachs of the new-born series (50 sq. mm. for each stomach), the average number

of glands per square millimeter was 121.36. The variation in the averages for the individual cases was less than five glands per square millimeter, ranging from 119.72 to 123.22. The range for this entire series was from 90 to 154 glands per square millimeter (Figs. 7 and 8).

There was no apparent increase in the number of glands in the new-born infants who had ingested food. Some of these had lived for several days and, so far as could be determined, they were in no way different from stillborn infants. The averages for the individual specimens are given in Table 9.

TABLE 8.—*Number of Glands in Stomachs of the Fetuses of the Ninth and Tenth Months*

Number	Calculated Age in Fetal Months	Area of Gastric Mucosa in Sq. Cm.	Average Number of Gastric Glands per Sq. Mm.	Estimated Total Number of Glands
19	8.11	19.66	77.72	152,844
11	8.16	30.58	78.62	240,443
37	8.20	31.58	78.18	246,915
33	8.90	33.91	84.08	285,165
Average	8.34	28.93	79.65	231,341
24	9.04	32.13	92.10	295,990
34	9.10	31.08	108.10	336,050
31	9.37	33.19	113.36	376,275
Average	9.17	32.13	104.52	336,105

TABLE 9.—*The Estimated Total Number of Glands in the Stomachs of Fourteen New-Born Infants*

Number	Area of Gastric Mucosa in Sq. Cm.	Average Number of Gastric Glands per Sq. Mm.	Estimated Total Number of Glands
1	.....	122.12	.....
2	34.85	120.54	420,081
3	27.38	120.76	330,677
4	35.35	121.10	428,185
5	35.78	121.22	433,761
6	41.66	121.66	506,908
7	38.75	122.36	474,145
8	46.91	123.22	578,098
9	45.25	122.40	553,957
10	71.84	120.68	866,977
12	39.99	121.34	485,250
13	32.51	119.72	389,281
15	39.58	120.58	477,291
25	34.41	121.46	418,016
Average	40.81	121.36	489,432

It appears from an examination of Table 11 that the development of the glands in number *per given area* is temporarily retarded from birth until the age of 2 months, there being only a very small increase during this time in the average number of glands per square millimeter. At birth, the average number of glands is 121.36 and at two postnatal months it is only slightly higher (128.28 glands per square millimeter). Between 2 and 5½ months the average number of glands per square millimeter is increased to about 181. Between the ages of

7 and 17 months there is an enormous growth in the number of glands per given area, the increment being about 225 per cent. The glands found at these ages and to the age of 6½ years are much smaller in caliber than they are at earlier and later periods, the mucosal connective tissue is practically obliterated and the glands are packed together very closely. It is during these years of childhood that the peak in number of glands per given area is reached (Tables 10 and 11 and Fig. 6).

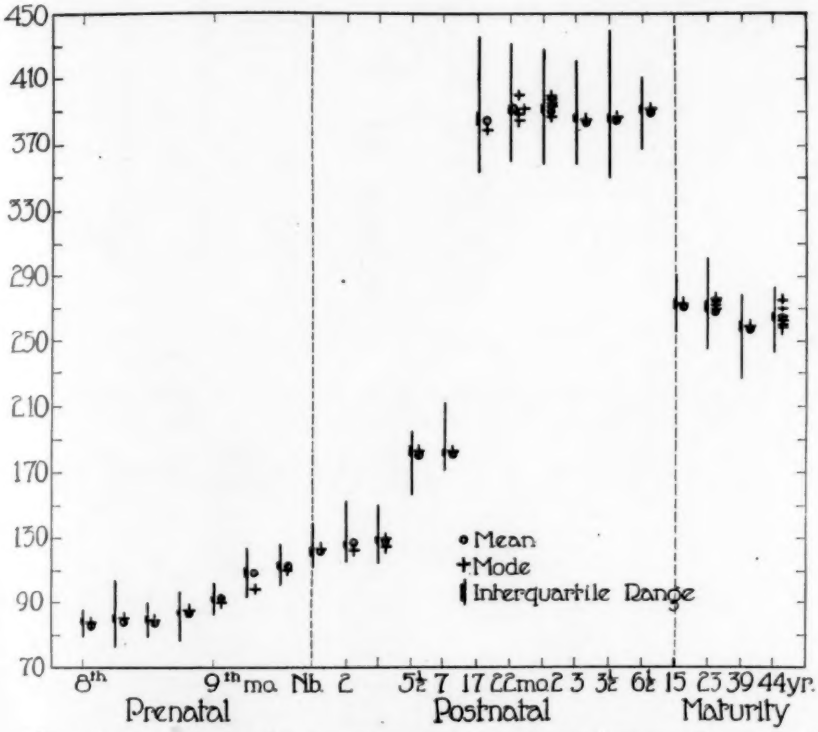

Fig. 6.—A graph showing the range, mean, mode and interquartile range of the entire series of observations made on the number of gastric glands per square millimeter. Ordinates: number of gastric glands per square millimeter. Base line: ages of persons.

From the age of 6½ to 15 years, the number of glands per square millimeter shows a decrease of nearly one-third. The exact time at which this decrease takes place has not been accurately determined, but it is evident that the major portion has occurred before 15 years, although the adult stomachs seem to show a slight decrease from the number found in the adolescent. It is possible that the variation shown in the last two adult specimens (Cases 38 and 26) in Table 11 indicates some further drop in numbers, but the relatively small amount of data at

TABLE 10.—*Range, Interquartile Range, Semi-Interquartile Range and Average Calculated from Raw Data on the Number of Gastric Glands Per Square Millimeter*

Number	Age	Average Number of Glands per Sq. Mm.	Minimum Number	Maximum Number	Total Range	Interquartile Range	Semi-interquartile Range
19	8.11 fetal months	77.72	70	85	15	3.0	1.5
11	8.16 fetal months	78.62	63	104	41	3.0	1.5
37	8.20 fetal months	78.62	69	89	20	3.0	1.5
33	8.90 fetal months	84.08	67	97	30	2.5	1.25
24	9.04 fetal months	92.10	82	102	20	2.5	1.25
34	9.10 fetal months	108.10	93	123	30	3.0	1.5
31	9.37 fetal months	113.36	101	126	25	4.0	2.0
9*	Birth	122.40	112	139	27	4.0	2.0
22	2 months	127.30	115	152	37	3.0	1.5
28	2 months	129.26	114	150	36	4.0	2.0
21	5.5 months	180.50	157	195	38	6.0	3.0
14	7 months	182.12	171	212	35	2.5	1.25
30	17 months	385.76	352	435	83	8.0	4.0
39	22 months	392.22	350	432	73	7.0	3.5
43	2 years	389.90	357	428	71	7.5	3.75
27	3 years	384.70	357	421	64	7.0	3.5
32	3.5 years	385.86	349	440	91	5.0	2.5
29	6.5 years	390.72	367	392	25	5.0	2.5
42	15 years	272.64	256	291	36	6.0	3.0
41	23 years	269.92	245	301	56	5.5	2.75
38	39 years	258.88	227	279	52	6.0	3.0
26	44 years	264.92	243	283	40	6.0	3.0

* Case 9 is taken as a typical specimen from the new-born series.

TABLE 11.—*Number of Glands in the Stomach in Postnatal Life*

Number	Age	Area of Gastric Mucosa in Sq. Cm.	Average Number of Gastric Glands per Sq. Mm.	Estimated Total Number of Glands
22	2 months	113.33	127.30	1,442,732
28	2 months	162.35	129.26	2,098,536
Average	2 months	137.84	128.28	1,770,634
21	5.5 months	150.58	180.50	2,880,478
14	7 months	168.16	182.12	3,062,639
Average	6.25 months	163.87	181.51	2,971,558
30	17 months	213.41	385.76	8,232,758
39	22 months	167.58	392.22	6,572,962
43	2 years	230.91	389.90	9,006,438
Average	21 months	203.97	389.29	7,936,382
27	3 years	154.33	384.70	5,927,202
32*	3.5 years	.....	385.86	.....
Average	3.25 years	154.33	385.28	5,937,202
29	6.5 years	258.16	390.72	10,087,085
Average	6.5 years	258.16	390.72	10,087,085
42	15 years	657.91	272.64	17,937,421
41	23 years	543.50	269.92	14,670,152
38	39 years	542.08	258.88	14,033,452
26	44 years	470.66	264.92	12,468,809
Average	30.25 years	553.54	266.59	14,774,481

* The total number of glands and the total area of the mucosa in Case 32 are omitted since only a small piece of this stomach was saved at necropsy.

hand hardly justifies an absolute statement on this subject. It is true, however, that the adults and the 15 year old specimen (Case 42) show more variation than do the stomachs of the preceding members of the series. This may be significant when one considers that there were more glands per square millimeter being counted in the stomachs of the younger persons, and hence the probability of error was larger. The glands in the adult have increased in size, the lumen is narrowed and the mucosal connective tissue is confined to thin sheets encircling each group

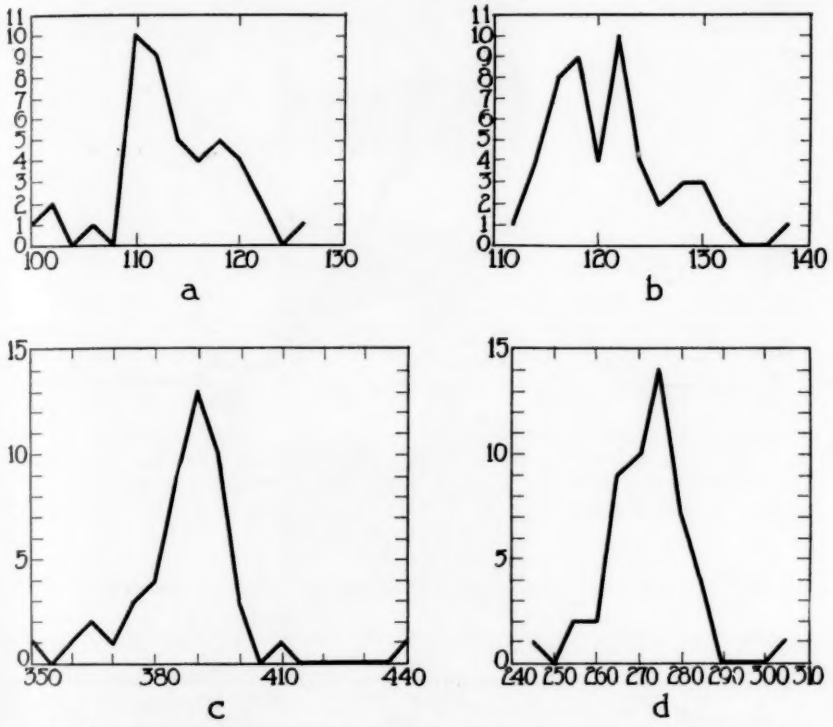

Fig. 7.—Four point-to-point frequency curves, each showing the distribution of fifty observations on the number of gastric glands per square millimeter. Ordinates: number of observations at given values. Abscissas: number of gastric glands per square millimeter; *a*, fetus of 9.37 months calculated age; *b*, typical full-term new-born infant; *c*, child aged 3½ years; *d*, adult, aged 23.

of glands and the membrana propria separating the individual elements. The glands have lengthened materially and are from two to three times larger than in early childhood. These changes are illustrated by Figure 9, which shows a series of vertical sections of the gastric mucosa at different ages.

Table 12, calculated from data given in Tables 8, 9 and 11, gives the number of gastric glands per crypt at the different ages studied. From

the ninth fetal month until the third month of postnatal life, the relation of about 2.5 glands per crypt is essentially the same. At 5½ and at 7 postnatal months, the number of glands per crypt is 3.35. From

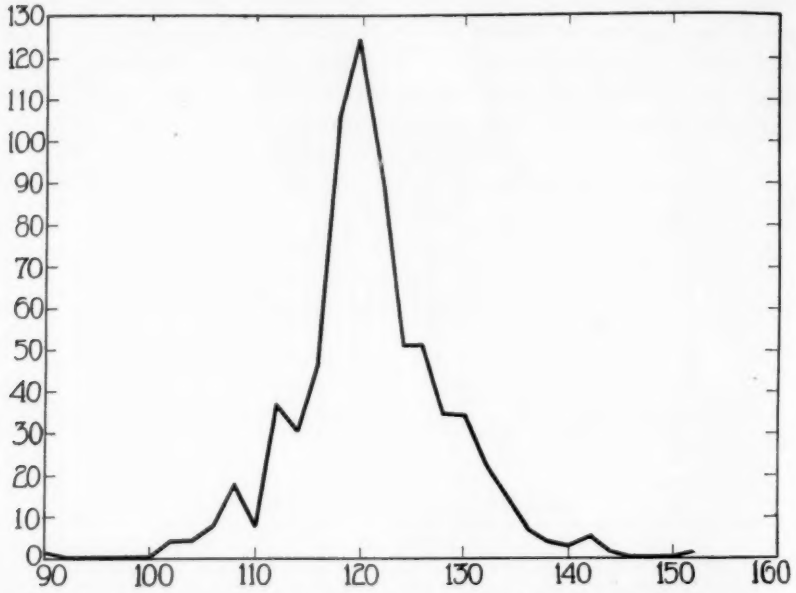

Fig. 8.—A point-to-point frequency curve showing the distribution of 700 observations on the number of gastric glands per square millimeter in fourteen new-born infants. Ordinates: number of observations at given values. Abscissas: number of gastric glands per square millimeter. Magnification, 60 diameters.

TABLE 12.—*Number of Gastric Glands per Gastric Crypt in the Individuals of Different Ages*

Age	Average Number of Crypts per Sq. Mm.	Average Number of Glands per Sq. Mm.	Average Number of Glands per Crypt
9 fetal months	33.04	79.65	2.41
10 fetal months	43.19	104.52	2.42
New-born	50.24	121.36	2.41
2 months	50.18	128.28	2.55
5.5 months	53.80	180.50	3.35
7 months	54.06	182.12	3.36
17 months	64.98	385.76	5.93
22 months	67.86	392.22	5.77
2 years	65.98	389.90	5.90
3 years	66.40	384.70	5.79
3.5 years	66.06	385.86	5.83
6.5 years	65.60	390.72	5.95
15 years	61.98	272.64	4.39
23 years	60.56	269.96	4.45
39 years	62.12	258.88	4.16
44 years	62.84	264.92	4.21

17 months to 6½ years the average is nearly six glands per crypt. In the older persons, namely, the 15 year old boy and the three adults, the average is about 4.3 glands per crypt.

B. GROWTH IN SURFACE AREA OF THE GASTRIC MUCOSA

Although this study was primarily concerned with the growth of both gastric crypts and glands, it was also necessary to calculate the surface area of the gastric mucosa at different ages, in order to estimate the total numbers of crypts and of glands in the viscus. This part of

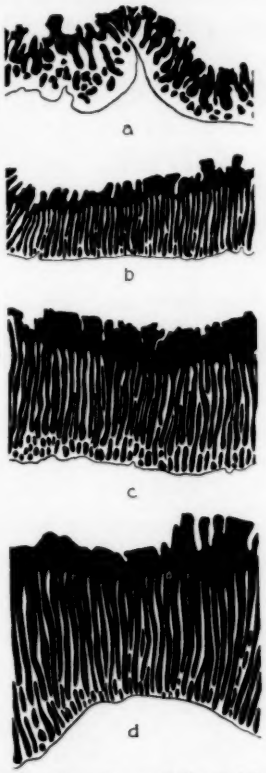

Fig. 9.—A series of projection drawings of the epithelial and glandular elements of the gastric mucosa: *a*, typical full-term new-born infant; *b*, child, aged 2 years; *c*, child, aged 6½ years; *d*, mature individual.

the study brings out some interesting features, particularly in comparison with the results of other workers. The publications of Toldt,[8] of Lissenko[19] and of Dargein[20] contain all of the available published records on gastric area. These data were brought together by Scammon,[21]

19. Lissenko, W.: The Growth and Structure of the Stomach in Childhood, Dissert., St. Petersburg, 1899, quoted from review in Jahresb. f. Anat. **3**:1900, and from Gundobin, A. P.: Die Besonderheiten des Kindesalters, Berlin, 1912, p. 264.

20. Dargein, P.: Surface et volume comparés du l'estomac et du duodenum, Bibliog. Anat. **7**:207, 1899.

21. Scammon, R. E.: Some Graphs and Tables Illustrating the Growth of the Human Stomach, Am. J. Dis. Child. **17**:395 (June) 1919.

who analyzed them and presented them in tabular form. Table 13 contains the data compiled by Scammon, with the present series added thereto. It is interesting to note that the data of Lissenko and Dargein, although widely differing in actual figures, follow the same type of curve of growth (Scammon).

In the present series, the surface area of the mucosa shows a rather rapid increase from 28.93 sq. cm. at nine fetal months to 40.81 sq. cm.

TABLE 13.—*Area of the Gastric Mucosa in Square Centimeters* *

Age	Area (in Sq. Cm.) of Gastric Mucosa According to			
	Present Series	Toldt	Lissenko	Dargein
8th fetal month	.....	23.02	.....	.....
9th fetal month	28.93	.....	.....	.....
10th fetal month	32.13	53.30	.....	.....
Birth	40.81	52.70	26.90	12.75
2 months	137.84	.....	60.20	31.00
3 to 3.5 months	.....	.....	67.70	48.00
5 to 5.5 months	159.58	.....	.....	55.00
6.5 to 7 months	168.16	.....	85.70	67.00
8 months	.....	.....	.....	82.00
9 months	.....	.....	125.70	.....
11 months	.....	.....	.....	118.00
1 year	.....	.....	133.90	.....
17 months	213.41	.....	.....	.....
22 months	167.58	.....	.....	.....
2 years	230.91	.....	.....	.....
3 years	154.33	.....	142.90	.....
6.5 years	258.16	.....	.....	.....
10 years	.....	505.10	.....	.....
15 years	657.91	657.70	.....	.....
Adult	518.74†	763.00	454.70	600.00

* The results obtained in this investigation are compared with the results of Toldt, Lissenko and Dargein.
† Average of three cases.

TABLE 14.—*Number of Times the Area of the Gastric Mucosa Increases from Different Ages to Maturity*

Age of the Individuals	Average Area of Gastric Mucosa in Sq. Cm.	Total Number of Times Increase to the Adult Period
9 fetal months	28.93	17.93
10 fetal months	32.13	16.14
New-born	40.81	12.71
2 months	137.84	3.76
5.5 months	159.58	3.25
7 months	168.16	3.08
17 months	213.41	2.43
22 months	167.58	3.09
2 years	230.91	2.24
3 years	154.33	3.36
6.5 years	258.16	2.00
15 years	657.91	—0.78
Adult	518.74	0.0

at birth. From birth to the third postnatal month the area increases nearly 3.5 times, rising from 40.81 sq. cm. to 137.84 sq. cm. After this period there appears to be a slow but steady growth until the seventeenth month, when the area is 213.41 sq. cm. Following this stage, the data fluctuate considerably but give evidence of a more or less steady increase.

Table 14 shows the number of times which the area of the gastric mucosa increases between the different ages in the developmental period and maturity. From the ninth fetal month to maturity there is an increase of nearly eighteen fold, from the tenth fetal month to maturity an increase of sixteen fold and from birth to maturity there is an increase of nearly thirteen fold. At 2 postnatal months this increase is nearly four fold, at 17 months it is 2.5 fold and at 6½ years it is but two fold.

Table 15 and Figure 10 show the number of times the area of the gastric mucosa increases from different ages to maturity as compared with the findings of Toldt,[8] of Lissenko [19] and of Dargein.[20] The absolute figures are quite at variance but all show the same general type of growth curve, as is indicated by the comparative histogram shown in Figure 10.

TABLE 15.—*Number of Times the Area of the Gastric Mucosa Increases from Different Ages to the Adult Period* *

Age	Number of Times Gastric Mucosa Increases from Each Age to Adult Period			
	Present Series	Toldt	Lissenko	Dargein
8th fetal month	.....	33.14	.....	.....
9th fetal month	17.93	.....	.....	.....
10th fetal month	16.14	14.31	.....	.....
Birth	12.71	14.47	16.90	47.05
2 months	3.76	.....	7.55	19.35
3 to 3.5 months	.....	.....	6.71	12.50
5 to 5.5 months	3.25	.....	.....	10.90
6.5 to 7 months	3.08	.....	5.30	8.95
8 months	.....	.....	.....	7.31
9 months	.....	.....	3.61	.....
11 months	.....	.....	.....	5.08
1 year	.....	.....	3.39	.....
17 months	2.43	.....	.....	.....
22 months	3.09	.....	.....	.....
2 years	2.24	.....	.....	.....
3 years	3.36	.....	3.18	.....
6.5 years	2.00	.....	.....	.....
10 years	.....	1.51	.....	.....
15 years	—0.78	1.16	.....	.....
Adult	0.00	0.00	0.00	0.00

* Results obtained in this study are compared with data from Toldt, Lissenko and Dargein.

C. GROWTH IN THE TOTAL NUMBER OF GASTRIC CRYPTS AND GLANDS

The Gastric Crypts: The total number of crypts and glands in the stomach may be estimated by multiplying the number per unit area by the total area of the gastric mucosa measured in terms of the same unit. In the fetus of 8.11 months, the total number of crypts so calculated was 63,206 and in the fetus of 9.37 months it was 152,023, an increment of nearly 250 per cent. The main factor causing the increase in the total number of crypts for this period is the rapid growth in the total area of the gastric mucosa, which expands fully one-third in this time. The total number of crypts in the stomach of the new-born seems to be controlled primarily by the area of the mucosa. This area is quite variable, ranging from 27.38 to 78.14 sq. cm. in the specimens studied. The

stomach measuring 78.14 sq. cm. was nearly twice as large as the others of the series, but in spite of this enormous variation in size, the number of crypts per unit area is very constant.

Surface area then *apparently* does not control the distribution of the crypts, as no constant difference in their number per given area was observed in any member of the series. In other words, contraction or expansion of the stomach wall does not influence the number of crypts per unit area of gastric wall. What probably happens when a stomach is moderately expanded is a smoothing out of the rugae into a flat surface but with no actual expansion or stretching of the epithelium or epithelial

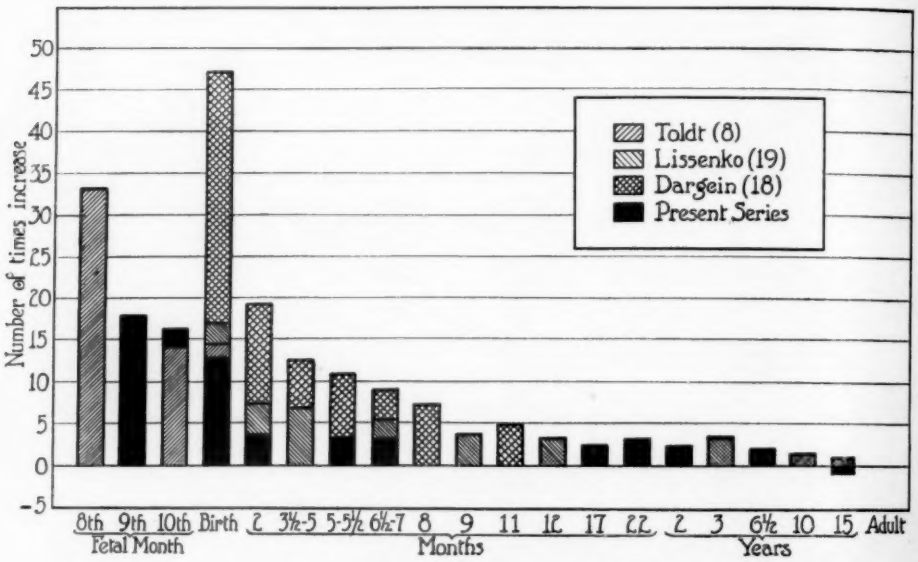

Fig. 10.—Comparative histogram, showing the number of times the area of the gastric mucosa increases from the eighth fetal month to maturity. Four sets of data are compared in this figure—that of Toldt, Lissenko, Dargein and the present series. Ordinates: number of times increase in the area of the gastric mucosa. Abscissas: ages of individuals.

bodies, the crypts or the glands. When the number of crypts per unit area is plotted against the area of the gastric mucosa in square centimeters, the result is nearly a horizontal line (Fig. 11), indicative of no correlation between these two factors. However, it is probable that hyperdistention of the stomach would change this relation. Experimental studies on this phase of the subject are now in progress.

It does not appear that the various parts of the stomach are in any way different with respect to the numbers of crypts. It is true that those present in the pylorus were somewhat more difficult to count accurately because of the villous processes in this region; when such

a count can be made it shows no marked departure from the average run of observations.

The average area of the mucosa in the neonatal series was 40.81 sq. cm.; the average total number of crypts 204,625. There was no apparent difference in the areas of the stomachs of the infants who had both lived and ingested food and those who were stillborn. By 2 months the total number of crypts has increased to an estimated number of 691,696 and at 5½ and 17 months this number is calculated to be 883,833. Between 17 months and 2 years the total number of crypts is calculated to be 1,282,529. From this period to 6½ years the total number of crypts is controlled primarily by the growth in surface area as no further increase occurs in their numbers per unit area.

By 6½ years, the total number of crypts has reached approximately 700,000. There is a steady increment in the total number of crypts

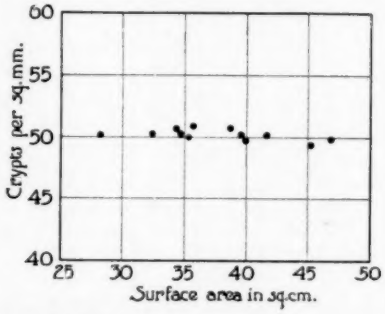

Fig. 11.—A field graph showing the relation between the surface area of the gastric mucosa and the number of crypts per square millimeter in the new-born series. Ordinates: number of crypts per square millimeter. Abscissas: surface area of the mucosa in square centimeters.

concomitant with the later increase in surface area of the mucosa. The slight increment in the number of crypts per unit area during infancy and early childhood apparently affects this to no great extent, although both factors must be considered as a part of the growth process. The total calculated number of crypts in Case 42, a boy, aged 15, is quite markedly higher than that of the adults studied, being 4,077,763. This case can only be explained on the basis of gratuitous variation, as this stomach was perfectly normal in every way. Scammon [21] has pointed out clearly the variability of the stomach in capacity and weight. The other three cases of this series seem to run more or less constant with regard to area. The large area of the mucosa in Case 42 makes the count of the total number of crypts for this stomach quite high. The average for the total calculated number of crypts in the three adult cases was 3,205,508.

The Gastric Glands: The rapid postnatal growth in number of gastric glands per unit area has a more profound influence on the increase in their total number than is the case with the crypts. This is especially true in early childhood. The average calculated total number of glands for the ninth month fetuses was 231,341, and for the fetuses of the tenth month was 336,105. Thus the increase in the glands in this period seems to run nearly parallel with that of the crypts. The variation in the total number of glands is not so marked as one would expect. The average calculated total number at birth is about 490,000. Case 10, the largest stomach of this series, gave a total estimated count of 866,977 glands. There was no decrease in the number of glands per square millimeter in this instance. The child

TABLE 16.—*Number of Times the Total Number of Crypts and Glands Increases from Different Ages to Maturity*

Age	Average Total Number of Crypts	Number of Times Increase to Maturity	Average Total Number of Glands	Number of Times Increase to Maturity
9th fetal month	96,041	33.37	231,341	59.32
10th fetal month	138,935	23.07	336,105	40.83
Birth	204,625	15.66	489,432	28.04
2 months	691,696	4.63	1,770,634	7.76
5.5 months	858,558	3.73	2,880,478	4.77
7 months	909,108	3.52	3,062,639	4.48
17 months	1,386,781	2.31	8,232,758	1.16
22 months	1,137,220	2.81	6.572,952	2.09
2 years	1,523,587	2.10	9,008,438	1.52
3 years	1,024,773	3.12	5,937,202	2.31
6.5 years	1,693,881	1.89	10,087,085	1.36
15 years	4,077,763	—0.78	17,937,421	—0.76
Adult	3,205,508	0.00	13,724,167	0.00

TABLE 17.—*Volume (Weight), Surface Area, Total Number of Crypts and the Estimated Total Number of Glands at Various Ages Expressed in Terms of Percentage of the Adult Figure for These Factors*

	Percentage of the Adult			
Age	Volume	Total Number of Crypts	Total Number of Glands	Surface Area
9th fetal month	2.6	2.8	1.5	5.2
10th fetal month	2.0	4.0	2.2	5.8
Birth	4.6	5.9	3.1	7.3
2 months	8.7	20.2	11.9	24.9
5.5 to 7 months	16.1	24.5	20.1	29.6
17 to 36 months	21.1	35.5	50.3	34.6
6.5 years	41.8	49.4	68.2	46.6
Maturity	100.0	100.0	100.0	100.0

was stillborn so the large size of the stomach was not due to the ingestion of food.

From birth until two postnatal months there is a rapid increase in the calculated total number of glands. From birth to this time, however, the surface area of the mucosa increases about three and one-half times. Evidently, then, there must be a rapid increase in the total number of glands in the stomach during this period, concomitant with the increase in the surface area of the gastric mucosa. The total

number of glands in the stomach at 2 months is approximately 1,770,000 (Table 10). At 5½ and at 7 months the calculated number has reached approximately 3,000,000. By 2 years this has been increased to about 8,000,000, and the total number at 6½ years approximates 10,000,000. By 15 years (Case 42) the total number of glands is in the neighborhood of 18,000,000. The area of the mucosa in this specimen was quite high compared with that in the adults examined; hence the total number of glands runs proportionately higher than in maturity. The average calculated total number of glands in the stomachs of the three adults was 13,724,167.

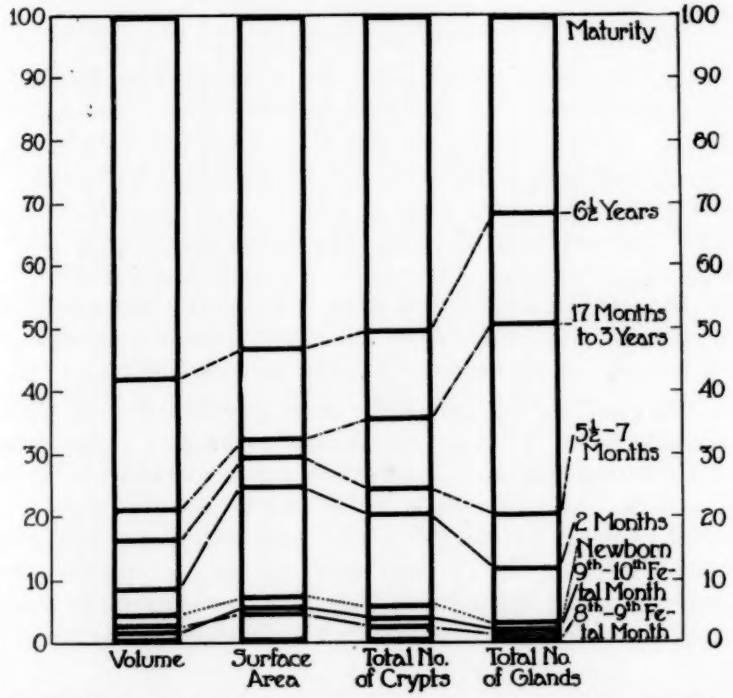

Fig. 12.—A graph showing volume (weight), surface area, total number of crypts and total number of glands at various ages, expressed as percentages of the average adult figures for these structures. Ordinates: percentages of the adult.

Table 16 shows the number of times the total number of gastric crypts and glands increase from different ages to maturity. From the ninth fetal month to maturity, the total number of crypts increases 33.37 times, while during the same period the glands increase 59.32 times. From the tenth fetal month to maturity the crypts increase twenty-three fold, and the glands forty fold. From birth to maturity the increase in crypts is about fifteen fold and the glands twenty-eight

fold. From two months to maturity the increase is markedly less, being 4.63 for the crypts and 7.76 for the glands. This decrease is more marked in respect to the number of glands than is the case of the crypts; it is due to the higher relative number of glands in early childhood.

Table 17 and Figure 12 show weight and surface area of the stomach, the total number of crypts and glands at different ages expressed in terms of percentage of the adult. The high percentages of the total number of glands from 17 months to 6½ years is due to the relatively larger number of glands per unit area at these ages as compared with the adult. This holds true in a lesser measure for the crypts.

V. SUMMARY

1. The number of gastric crypts per square millimeter of human gastric mucosa can be counted with accuracy if a proper technic is employed. There is a steady increase in the number of these structures per square millimeter in the latter part of fetal life. Following birth, there is a temporary arrest in the growth of number per unit area until the third postnatal month. After this time there is again a steady increase until 17 months. The number is constant through early childhood. Between 6½ and 15 years there is a drop of about one-eighth in the number per unit area. After this decrease there is no subsequent constant change in the number of crypts per unit area.

2. The gastric glands follow the same general course of development as the crypts. Their increase is rapid in the last two fetal months and their number per unit area remains fairly constant until 2 postnatal months. The increase is rather rapid (220 per cent.) up to 5½ to 7 months. From this period until 6½ years they remain practically constant. By 15 years there is a drop of one-third in the number per square millimeter. This value remains fairly constant thereafter, although there is some evidence of a slight decline throughout adult life.

3. The area of the gastric mucosa is a variable factor. In the four sets of data given its development follows the same type of curve. The surface area of the mucosa increases about thirteen fold between birth and maturity.

4. The total number of gastric crypts increases about sixteen fold between birth and maturity. The calculated average number in the new-born (thirteen cases) is 204,625; the calculated average number in the adult (three cases) is 3,205,508.

5. The total number of gastric glands increases twenty-eight fold between birth and maturity. The calculated average number in the

new-born (thirteen cases) is 489,432; the calculated average number in the adult (three cases) is 13,724,167.

6. The ratio of the number of glands per crypt shows a constant increase from the fetal period to middle childhood and then undergoes a decrease. From the ninth fetal month to 2 postnatal months it is about 2.5; at 5½ and at 7 postnatal months it is 3.3; from 17 months to 6 years it is nearly 6.0 and in the adolescent and the adult, approximately 4.3.

THE ROENTGENOGRAM IN EARLY SCURVY*

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There have been relatively few investigations from which effective help could be obtained in the roentgenologic diagnosis of early scurvy, particularly of the so-called borderline cases, except the excellent contributions of Fraenkel [1] and the recent contribution of Wimberger.[2] The subject merits attention because the number of cases of mild scurvy is certainly far greater than is commonly believed. Undoubtedly, there are instances of transient pains in the extremities, lack of appetite and loss of weight, pallor and even hemorrhagic manifestations which pass unrecognized and which usually clear up when a change is made to a more rational diet, not necessarily including orange juice.

Several such cases have come to our attention recently at this clinic, and we therefore decided to determine, if possible, how early a definite diagnosis of scurvy may be made by the roentgenogram and what the essential points in the picture permitting such a diagnosis should be. The investigation was based on a fairly large collection of roentgenograms from cases of scurvy in human beings (many of which have been followed serially for months) and on the findings of experimental scurvy in the guinea-pig.

EXPERIMENTAL SCURVY

Material.—The animals used for this purpose were all young, of the same litter whenever possible, and of approximately 250 gm. in weight. The diet producing scurvy was made up as follows: Soy beans, 50 per cent.; rolled oats, 25 per cent.; skimmed milk, 10 per cent.; yeast, 4 per cent.; butter, 5 per cent.; calcium carbonate, 1 per cent.; sodium chlorid. 1 per cent.

Of this mixture the animals received 15 gm. daily, together with filter paper for roughage and plenty of water. In order to prevent any complicating rachitic changes in the bones, the animals were given 0.5 c.c. of cod liver oil daily. The success of this procedure was shown by the absence of osteoid tissue in microscopic sections from experimental animals and by the lack of development of any bone lesions in

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* From the Department of Pediatrics, Harvard Medical School, and The Children's and Infants' Hospitals.

1. Fraenkel: Fortschr. a. d. Geb. d. Röntgenstrahlen **7**, 1903-1904; ibid. **10**, 1906-1907.

2. Wimberger, H.: Ztschr. f. Kinderh. **36**:279, 1923.

control animals when a sufficient amount of orange juice was added to the foregoing diet.

Subacute and chronic scurvy were produced by the addition to the diet of small amounts of orange juice (up to 2 c.c. daily) after the animals showed definite clinical and roentgenographic symptoms of the acute stage.

DIAGNOSIS OF SCURVY IN GUINEA-PIGS

The clinical diagnosis of scurvy in guinea-pigs is a relatively simple matter, for the symptoms are striking and uniform in all of the animals. The first sign (usually occurring after the second week) is often an unwillingness to move. The animals sit huddled in a corner of the cage for long periods. When stimulated to move, it is noticed that the greatest difficulty with motion is usually in the hind legs. Loss of appetite and consequent slow loss of weight occur at about the same time. The coat becomes ruffled and loses its shiny appearance. Tenderness of the joints is an early symptom; often swelling and hemorrhages may be noticed. The teeth frequently become loosened or break. Chick and his co-workers have described the "scurvy position," which is a lifting of the leg to protect the affected joint.

While these symptoms are adequate to make a definite diagnosis of scurvy in the guinea-pig, it is difficult, if not impossible, to judge by them the progress of the disease or the stage in which an animal may be at a given time, since the time of appearance of joint pain, hemorrhages, loosening of teeth and other symptoms varies greatly in these animals and is to a certain extent dependent on the physical condition of the animal at the beginning of the experiment, as well as on its age, weight and activity.

We have, therefore, developed a method of roentgenographic diagnosis which we believe is much more accurate and satisfactory than mere clinical observation. The roentgenologically demonstrable changes in the long bones of guinea-pigs are not sufficiently clear-cut to serve this purpose. A thinning of the cortex and decreased opacity of the shaft is all that can be regularly observed. However, the costochondral junctions offer an ideal substitute, for there the changes are precise, occur early and are readily demonstrated. The method consists merely in taking a posterior-anterior oblique or a lateral picture of the thorax in such a way that the right or the left costochondral junctions are nearest to the plate. The first six or eight thoracic ribs are always most severely affected, and it is therefore necessary to extend the front legs beyond the head and hold the animal in a position of opisthotonos in order to get a clear picture of the upper portion of the thorax.

We have followed a series of animals by this method and have been able to differentiate between acute, chronic and healing scurvy.

THE HISTOLOGIC AND ROENTGENOGRAPHIC CHANGES OF SCURVY IN GUINEA-PIGS

To obtain a clear conception of the changes in the roentgenogram which are due to scurvy, it is important to appreciate the nature of the underlying pathologic processes in the bone, such as the disturbance in growth and the differences in calcium deposition. For the purposes of our explanation the chief processes in the normal growth of bone may be recalled. The normal growth of a long bone proceeds in two directions and is brought about by two entirely different biologic mechanisms. Growth in width is due to the laying down

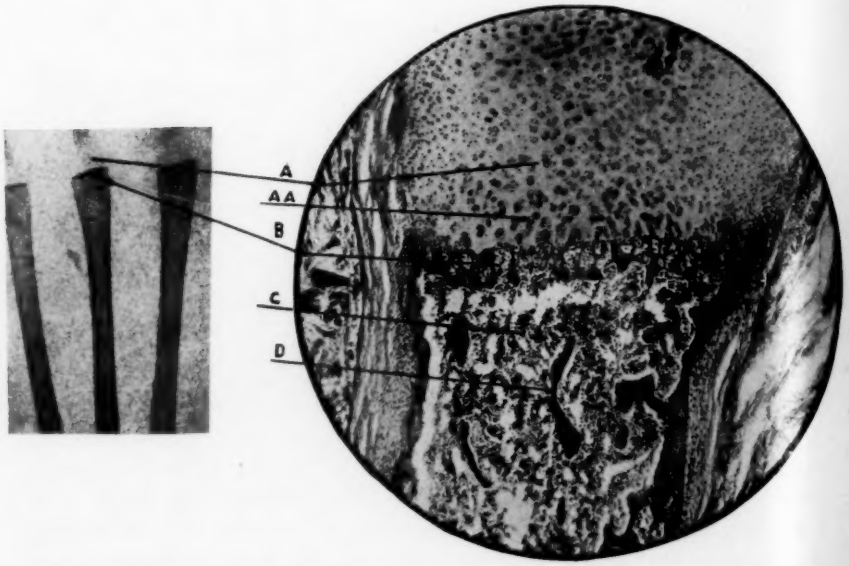

Fig. 1.—Guinea-pig No. 4 L. B., normal. Roentgenogram and frontal section (low power magnification) fourth thoracic rib; *a*, cartilage; *b*, primarily calcified cartilage; *c*, lymphoid marrow; *d*, bone.

by the periosteum of successive lamellae of bone on the external surface of the shaft, and the continual resorption of calcium from within the marrow cavity by osteoclasts as well as by chemical halisteresis.[3] This growth, therefore, is a finely balanced process of deposition and resorption, resulting at once in the widening of the bone and the widening of the marrow cavity. Growth in length proceeds along entirely different lines. The cartilage cells of the epiphysis (Fig. 1 *a*), passing first through a stage of proliferation (*a a*), become arranged in rows and the intercellular matrix becomes calcified (*b*). This calcified cartilaginous matrix represents histologically the zone of temporary calcification, and

3. Tanaka: Biochem. Ztschr. **35**:113, 1911.

roentgenographically the epiphyseal line. Blood vessels from the marrow cavity enter this zone of temporary calcification, destroy the cartilage cells and remove a part of the calcified matrix. That part of the calcified matrix which is not destroyed remains to form the osseous trabeculae of the new spongiosa (*d*). These trabeculae in turn become covered by osteoblasts and are strengthened by an additional deposit of calcium.

While the process of resorption goes on from below, new cartilage cells arrange themselves in rows above the zone of temporary calcification and their matrix becomes calcified. Here again, growth is a

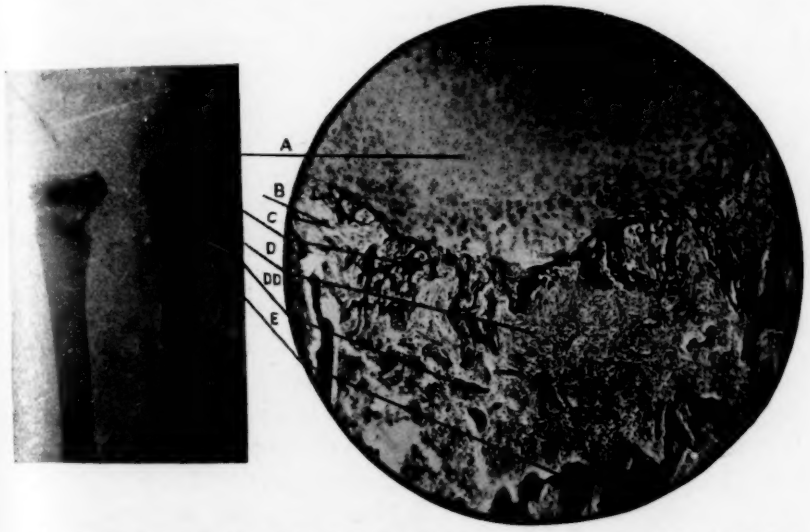

Fig. 2.—Guinea-pig No. 3 D. B., chronic scurvy (manifestus mitior). Roentgenogram and frontal section (low power magnification) fourth thoracic rib; *a*, cartilage; *b*, homogeneous scorbutic new bone; *c*, primarily calcified cartilage; *d*, framework marrow; *e*, old bone.

finely balanced process of deposition and resorption. The same endochondral type of growth takes place at the centers of ossification of the epiphyses.

A comparison of this normal endochondral growth with the growth in scorbutic bone (Fig. 2) shows a number of striking differences. The zone of proliferating cartilage cells has become distorted and evidence of mitosis is lacking (*a*). The zone of temporary calcification (*c*) has become several times broader than normal and is well calcified although much distorted. The blood vessels from the marrow cavity which normally invade this area are few and small, apparently wander aimlessly about and do not enter the cartilage to carry on the normal processes of resorption. On the shaft immediately back of the zone

of temporary calcification is a zone of greatly weakened new bone. The spongiosa, formed at the period when the scorbutic process was slowly retarding the formation of new bone, is extremely weak. It consists of trabeculae of poor quality (*dd*) which are no longer covered by osteoblasts, or, if osteoblasts are present, they are small, of poor staining quality and obviously nonfunctioning. The trabeculae have received no additional calcium. The lymphoid marrow of the normal bone is here replaced by the so-called framework marrow, consisting chiefly of connective tissue (*d*). As will be seen from Figure 2, the broadened zone of temporary calcification corresponds to the broadened epiphyseal line in the roentgenogram, while the area of weakened new bone immediately adjoining it represents the area of decreased density which is commonly spoken of as the "Trümmerfeldzone." [4] The changes produced by scurvy at the centers of ossification of the epiphyses are essentially the same. Here the same broadening of the zone of temporary calcification occurs, and this is an important factor in the explanation of the roentgenogram.

The roentgenologic changes in the epiphyses of the bones in scurvy have been explained on the basis of a disturbed balance between calcium deposition and resorption; the deposition supposedly lagging behind, while resorption goes on normally. It seems to us, however, that such an explanation does not cover the facts as observed in microscopic sections or roentgenogram, for the cartilaginous matrix at the epiphyseal junction, and also at the center of ossification of the epiphyses, is as well calcified and broader—though more irregular and distorted—than in the normal bone. In other words, calcium deposition at these points is certainly not interfered with.

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4. The term "Trümmerfeldzone" or "Trümmerzone," which is extensively used in the German literature and which has found its way into the American roentgenologic vocabulary, is omitted in this discussion for two reasons: First, a good deal of confusion exists as to the region to which this term is applicable. Wimberger, for instance, speaks of the calcified cartilaginous matrix of the epiphyseal line as the "Trümmerfeldzone." Among American pediatricians and roentgenologists the idea, justly, is prevalent that this term refers to the area of decreased density on the shaft immediately back of the broadened epiphyseal line. Secondly, this term, which literally means "zone of destruction" or "zone of chaos," was originally coined to describe the roentgenographic changes at the epiphysis which were thought to be at least partly due to external trauma. This is, of course, true of the advanced cases of scurvy, but not of the early cases which yet show these typical roentgenographic signs. In other words, the changes at the epiphyses are due to an orderly pathologic process and no more constitute a zone of destruction than any other part of the bone. For the sake of clearness we shall speak of these changes merely as the "broadened epiphyseal line." For the area of decreased density on the shaft immediately adjoining the broadened epiphyseal line, we propose the term "scurvy line," which, we believe, combines the advantages of simplicity and accuracy.

Granting that scurvy is a disease of actively functioning cells throughout the body,[5] we need merely to recall that calcium deposition and resorption are of two types—chemical and cellular—and to postulate that the cellular mechanism of deposition or resorption will be disturbed, while the chemical processes will continue unimpaired, for, so far as we know, in scurvy the calcium metabolism as such is normal.

The cellular mechanism of deposition is illustrated by the activity of osteoblasts, and resorption by the activity of osteoclasts, or, what is still debated, the capillaries. The chemical processes of deposition are illustrated by calcium deposition in cartilaginous matrix at the epiphyseal line as well as at the center of ossification of the epiphysis. The chemical process of resorption is general throughout the bone (halisteresis—Tanaka).

The changes in calcium distribution in scurvy are explicable on this basis. At the zone of temporary calcification, deposition is a chemical process and, therefore, undisturbed. Resorption from this area is cellular, therefore interfered with, and results in the broadening of the calcified zone. The same is true of the periphery of the epiphyseal centers. In the shaft, deposition of additional calcium is exclusively cellular—and fails. Resorption is both cellular and chemical; the chemical process continues undisturbed and results in the disappearance of the trabeculations and the thinning of the cortex.

THE ROENTGENOGRAM IN SCURVY IN HUMAN BEINGS

Method of Investigation.—Keeping in mind the changes found in experimental scurvy, we examined the roentgenograms of the patients in our collection and further followed serially a number of cases in our wards. In order to determine what changes in the roentgenogram are distinctive of early scurvy, we began with a series of well-advanced, unquestionable cases, noting the roentgenologic characteristics, and then worked down through less and less pronounced cases until the borderline cases were reached. In this manner we observed the time of appearance and the relation to each other of the various changes from the normal.

As in rickets and in other disturbances of bone growth, the most striking changes of scurvy are seen in the regions of greatest growth impulse, such as the proximal end of the humerus, the distal ends of the bones of the forearm, the distal end of the femur, and the proximal ends of the tibia and the fibula. For some reason, not yet clear, scorbutic changes are much more severe in the lower extremities, while those of rickets are more easily demonstrated in the arms and particularly in

5. Höjer, J. Axel.: Acta Paediat. **3,** Suppl., 1924.

the wrists. The most satisfactory plates for the study of scurvy are, therefore, those showing the knee.

The Roentgenogram of a Normal Bone.—For purposes of comparison, the roentgen-ray appearance of a normal bone might here be briefly discussed. At birth and during the first half year of life, no centers of ossification of the epiphyses (except that of the distal humeral epiphysis) are sufficiently calcified to cast a shadow on the roentgenogram. The shaft, however, is completely calcified and shows the following characteristics: a very even density, a sharply defined cortex, which may be from one-fifth to one-third of the diameter, and a series of fine, closely packed parallel lines, somewhat more prominent near the extremity than in the middle of the shaft, representing the osseous trabeculae. At the epiphysis on either end there is a narrow, sharply pencilled white line of greater density than the remainder of the shaft. This line represents the zone of temporary calcification—the area of calcified cartilaginous matrix. It is denser than the shaft because, when the new bone is formed from this calcified matrix, a large part of the calcium is again absorbed.

There are, then, four principal roentgen-ray criteria of a normal bone: (1) a sharp, narrow line at the end of the shaft; (2) a broad, clearly defined cortex; (3) even density of the entire shaft, and (4) fine trabeculations throughout.

When calcification has occurred in the center of the epiphysis, this area is of the same density as the shaft, is sharply circumscribed and shows slight trabeculation throughout.

The Roentgenogram of Scorbutic Bone.—The picture of the bones of a well advanced, uncomplicated case of acute scurvy—even without subperiosteal hemorrhages—is so characteristic that it may be diagnosed at the first glance. The epiphyseal line becomes two or three times as wide as the normal bone, and has a finely irregular appearance. This line often shows a characteristic step-like lateral projection in the roentgenogram. There is usually also an area of decreased density on the shaft, immediately back of the epiphyseal line. This area (for which we proposed the term "scurvy line" since it is pathognomonic of this condition), represents the region of the newly formed spongiosa in which calcium deposition has slowed up or ceased.

The appearance of the shaft of the bone in scurvy has never received the attention it deserves. As a matter of fact, it is fully as characteristic as any of the other roentgenographic changes in this condition. The cortex, which in a normal bone is usually from one-fifth to one-third the thickness of the shaft, becomes very much narrowed and in most cases is represented by only a fine, sharply pencilled line. The remainder of the shaft is still more characteristic, because the dis-

appearance of the trabeculations gives it a curious smooth, transparent aspect—somewhat like ground glass. The shaft of a rachitic bone also shows a decreased density, but here the trabeculations are distinctly seen and are even coarser and more irregular than in normal bone. This difference between the shafts of scorbutic and rachitic bones is well shown in Figures 3 and 4. That the disappearance of trabeculations from the shaft in scurvy is not merely due to atrophy consequent on disuse of the extremity, follows from the fact that even the earliest cases of this condition, in which little or no limitation of activity had occurred, show this change unmistakably. Furthermore, a truly atrophic bone,

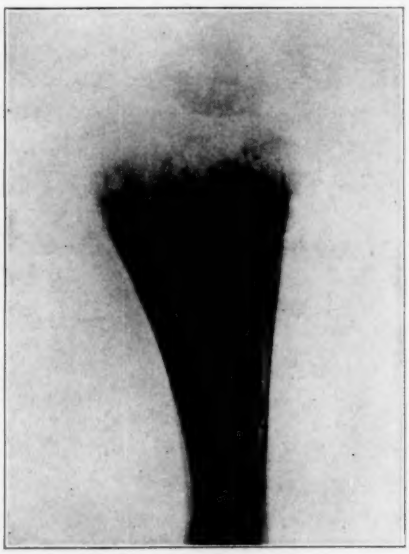

Fig. 3.—Rachitic bone. Note that the changes are directly opposite to those occurring in scurvy. Coarsening of trabeculation on the shaft, disappearance of the epiphyseal line and fading of the edge of the epiphyseal center.

such as is seen in poliomyelitis for example, retains distinct trabeculations although the calcium content of the whole bone is much decreased.

Another characteristic feature of scurvy [6] is shown at the edges of the centers of ossification in the epiphyses of the long bones. This is a circular shadow surrounding these centers, which, with regard to intensity, corresponds to the shadow of the epiphyseal line. It is, in fact, produced in exactly the same way. Histologically also the condition here is the same as at the end of the shaft—broadening and damage of the preparatory zone of calcification and weakening of the primary spongiosa. Here, too, the usually sharp and narrow edge of the epi-

6. Wimberger, H.: Footnote 2.

physeal center is broadened and has the same finely irregular appearance as at the end of the shaft. The edge nearest the joint is usually broadest, due to the fact that growth is more rapid on that side.

In our material, we have been able to confirm Wimberger's statement that this circular shadow is almost invariably present in scurvy, that it represents one of the most characteristic features of the roentgenogram of this disease, and that it is found in no other condition of disturbed bone growth. The edging of the epiphyseal centers which is sometimes seen in atrophic bones is always narrow, sharply defined, and lacks the finely irregular appearance of the characteristic shadow in scurvy.

Subperiosteal hemorrhages are of little interest in this discussion. They are seen roentgenologically only in healing scurvy and occur characteristically near the epiphyses. It is said, in fact, that all the blood of these extravasations comes from the epiphyseal line in which damage from trauma is greatest and in which the vessels of the marrow cavity come close to the surface and are injured. In our own collection we find no picture of subperiosteal hemorrhage in which the extravasation is not connected with, and heaviest at, the epiphyseal line. At any rate, the first roentgenologic evidence of subperiosteal hemorrhage is swelling of the soft tissues and often a small spur at the protruding lateral edge of the epiphyseal line.

The essential points in the roentgenogram of a well developed case of scurvy are, therefore, the following:

1. A finely irregular, broadened, well-calcified epiphyseal line.

2. A small spur at the lateral edge of the epiphyseal line. Occasionally dislocation of the entire epiphysis.

3. An area of decreased density (scurvy line) immediately back of the epiphyseal line, which represents lack of calcification of the newly formed spongiosa.

4. A very thin cortex, often merely a narrow white line.

5. Glass-like transparency of the shaft. No trabeculations seen as in normal bone or in rickets.

6. A broad, finely irregular white edge on the epiphyseal center of ossification of the long bones.

Less advanced cases of scurvy show practically all of the beforementioned changes except the lateral spur of the epiphyseal line. This spur is apparently the last addition to the scorbutic damage in the bones and marks the stage at which the weakening of the zone of temporary calcification has become so great as to permit a pushing out of some of its substance laterally, or a lateral displacement of the entire epiphysis, by very slight trauma.

Clinically, the cases which show the lateral spur are usually far advanced, with tremendously swollen and painful extremities and all the other usual symptoms of scurvy. The cases in which the spur is lacking, but the broadened epiphyseal line, the scurvy line, the ground glass appearance of the shaft and the edging of the epiphyseal center are present (Fig. 4, *a*) offer no difficulty in clinical diagnosis but are not so far advanced as the cases showing the spur. In other words, the scurvy line which represents the newly formed weakened spongiosa, is evidence of moderately advanced scurvy. The lateral spur of the epiphyseal line is evidence of a full-blown, advanced case.

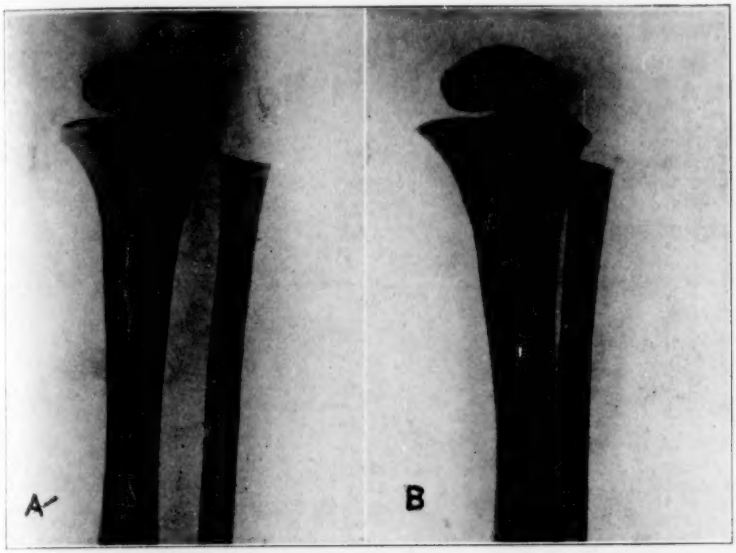

Fig. 4.—Moderately advanced case of scurvy. (*a*) Note the irregular edge of center of ossification of epiphysis; broadened, well-calcified epiphyseal line; scurvy line, and absence of trabeculations on shaft; (*b*) same case, healed. Note the sharper outline and broadening of edge of epiphyseal center; broadening of epiphyseal line due to calcification of scurvy line; reappearance of trabeculations on shaft.

The borderline case of scurvy usually shows only three of the characteristics before mentioned, namely: the broadened epiphyseal line, the dense shadow around the center of ossification of the epiphysis and the absence of trabeculations in the shaft (Fig. 5). The scurvy line and the lateral spur are absent. It is necessary here to emphasize the importance of considering the whole picture rather than the individual signs. Any one of these signs may possibly be found in conditions other than scurvy; the combination of the three (or even the absence of trabeculae in the shaft and the edging of the epiphyseal center alone) is pathognomonic of this disease. In other words, the diagnosis of scurvy can

with certainty be made on these three signs, even in the absence of the much abused scurvy line. In fact, the great importance placed on the roentgenographic evidence of the area of weakened spongiosa in the diagnosis of scurvy is responsible for the failure of the roentgenologic recognition of the earliest cases.

The temporal relation of the changes demonstrable in the roentgenogram to the early clinical symptoms of scurvy is such as to eliminate practically the borderline cases, for whenever the most suggestive clinical symptom of scurvy (pain in the lower extremities) appears, the roentgenogram gives unmistakable evidence of the presence or absence of this

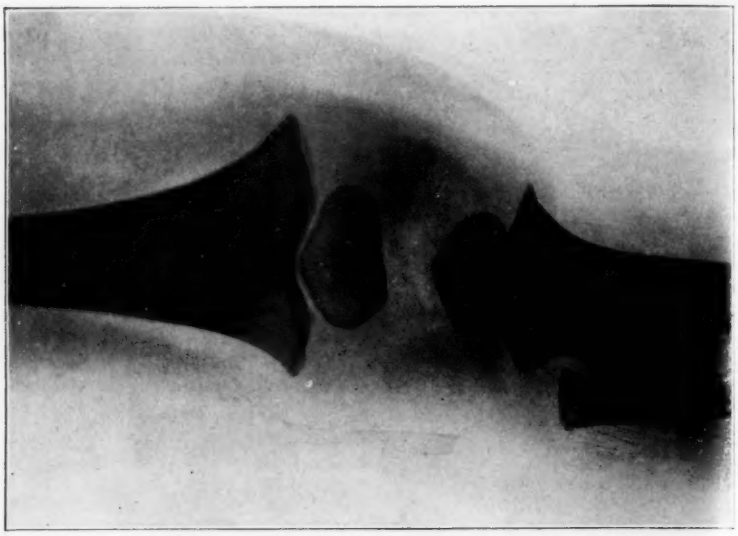

Fig. 5.—Borderline case of scurvy. Clinically doubtful. Note the significant combination of signs; absence of trabeculations on shaft; broadened epiphyseal line; edging of center of ossification of the epiphysis.

condition. The same is true of experimental scurvy in the guinea-pig: the first clinical symptoms of scurvy in guinea-pig No. 3 L. B. were (if a loss of weight for two days be disregarded) a slight ruffling of the coat and an unwillingness to move, noticed on the nineteenth day of the experiment. A roentgenogram of the living animal showed suggestive changes at the costochondral junctions. The animal was killed on that day and the roentgenogram of the dissected thoracic wall showed clear evidence of acute scurvy (Fig. 6). Because of the small size of the ribs in the guinea-pig, these early signs are difficult to demonstrate in the living animal. In the infant the bones are sufficiently large to permit such a demonstration, and Patient R. H. is a case in point. This was a baby, aged 11 months, admitted to the Infants' Hospital for pain in

the legs of one week's duration. No symptoms whatsoever had been noted before that period. The baby had been fed on a formula of cow's milk, boiled, and had received cod liver oil and orange juice since the second month. When questioned as to the amount of orange juice administered, the mother stated that the baby was given "a whole orange to suck" about every third day, but admitted that at times these intervals were rather irregular. The physical examination was negative except for tenderness of the lower part of the legs and unwillingness to stand. There were no changes in the gums, no hematuria and no other hemorrhagic manifestations. A report from the Roentgen-Ray Department, dated August 14, reads: "A film of the knees shows no evidence of scurvy." And again, August 15: "Reexamination of knees and legs still fails to show any evidence of scurvy." The baby recovered completely during a stay of ten days and was discharged with the diagnosis of "scurvy (questionable)."

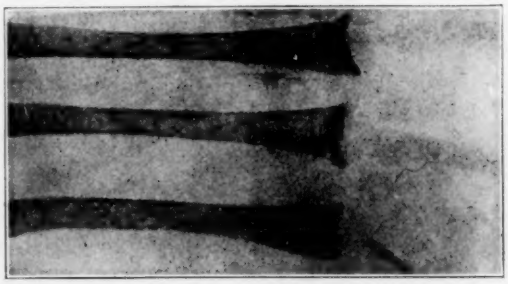

Fig. 6.—Acute scurvy. Guinea-pig No. 3 L. B., upper thoracic ribs. First day of clinical symptoms, nineteenth day of experiment.

In the light of our investigation, a review of the first roentgenogram of this patient left no doubt that the condition in question was actually scurvy. Figure 5 shows the roentgenogram taken one week after the first clinical symptom was noticed. The absence of trabeculations in the shaft, the broadened, finely irregular, well calcified epiphyseal line and the distinct ring around the center of ossification of the epiphysis, taken together, are pathognomonic of scurvy. No area of decreased density back of the epiphyseal line was demonstrable in any of the plates, for this is a sign which occurs much later than the broadening of the line.

THE NEW "BORDERLINE CASE" OF SCURVY

It seems logical to us that radiographic changes should be demonstrable before the appearance of the earliest clinical evidence of scurvy (pain), because "scurvy generally takes from six to nine months to become manifest" (Hess), which affords ample time for bone changes to appear, and it would be folly to argue that the changes in the roent-

genogram of the case of R. H., described in the foregoing, had occurred during the short week of clinical symptoms. Furthermore, the pain and unwillingness to move are not the cause but the consequence of the lesions in soft tissue and bone.

The hitherto little appreciated specificity of the triad of roentgenograhic signs of early scurvy (broadened epiphyseal line, edging of center of ossification of the epiphysis, and, especially, the ground-glass appearance of the shaft), and the possibility to demonstrate the presence of scurvy by the roentgenogram before the accepted clinical symptoms of pain or hemorrhage have occurred, place the "questionable" case of scurvy back among those which at present pass merely as nutritional disturbances, with pallor and loss of weight for a number of weeks or perhaps months as the sole symptoms. Persistent roentgenographic examinations of such patients, especially of those in whom there is a history of feeding on boiled milk without orange juice, will now and then unquestionably reveal a case of scurvy which, if pain or hemorrhagic manifestations were depended on, would be recognized possibly only a number of weeks later.

SIGNS OF REPAIR

The roentgenographic signs of healing scurvy are fully as characteristic as those of the acute process. Healing scorbutic bone shows marked improvement from one to two weeks after the beginning of treatment. At first the broadened epiphyseal line loses its finely irregular appearance and becomes sharply outlined; the scurvy line not only disappears but becomes more heavily calcified than the remainder of the shaft (Fig. 7). This adds additional breadth to the epiphyseal line (Fig. 4, *b*). Later the cortex of the bone becomes stronger, trabeculation becomes distinct, and after months nothing remains of the old process except a wide, often double, line of ossification in the shaft near the end where the old process had been active. This double line is due to the fact that, as growth proceeds, the heavily calcified old scurvy line moves further and further away from the epiphyseal line. The calcified scurvy line may often be seen in the shaft years after the process has healed.

The epiphyseal centers of ossification show healing scurvy most typically. A rapid growth sets in, the edges lose their finely irregular appearance and become very broad. Here again a double line of calcification is often found, and is due to the same factors as the doubling at the epiphyseal line.

The organized and calcified hematoma in scurvy grows with the bone. This means that the cartilage of the eiphysis is broadened to cover the surface of the hematoma as well. If the epiphysis is displaced, the bone

and hematoma will grow in such a way as to bring again the epiphysis into the center of the axis of the shaft, even though the new bone for the greater part has to be formed from the hematoma.

The subject of healing scurvy is by no means adequately presented by these few remarks. It is as extensive as that of the acute stage and susceptible of the same method of investigation, although for our purposes it did not seem essential to present it more fully.

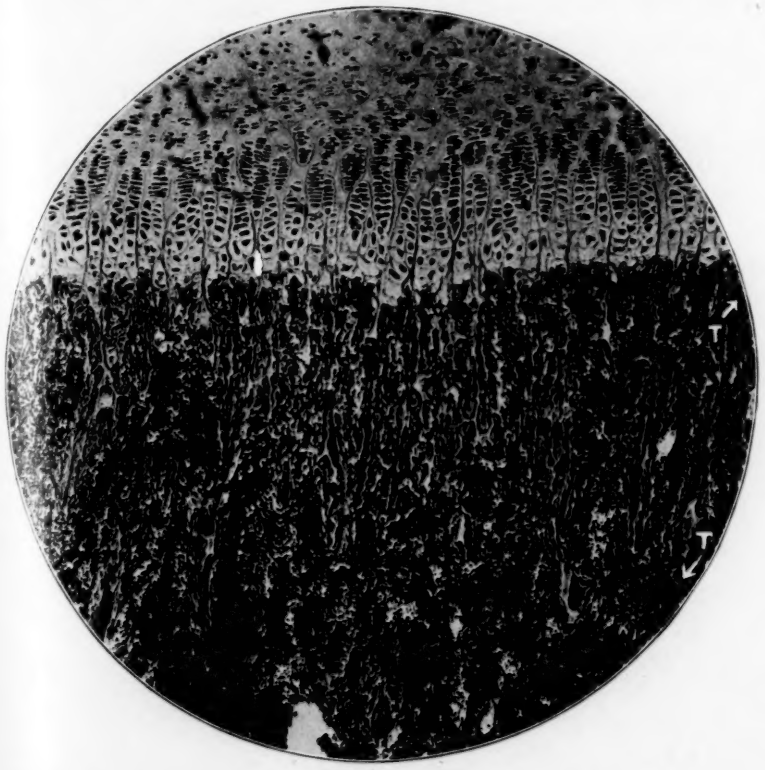

Fig 7.—Healed scurvy. Guinea-pig No. 3 Y. Frontal section (low power magnification), fourth thoracic rib. Compare with Figure 1 and note heavy calcification of new osseous trabeculae (*t*), which is responsible for widening of epiphyseal line, Figure 4, *b*.

CONCLUSIONS

1. The ground-glass appearance of the shaft, which is due to the disappearance of trabeculae, is an important and hitherto underestimated roentgenographic sign of scurvy.

2. We can support Wimberger's claim that the edging of the epiphyseal centers is a constant and reliable sign of scurvy.

3. The combination of broadened epiphyseal line, edging of the epiphyseal center and disappearance of trabeculations in the shaft is pathognomonic of this disease.

4. The term "Trümmerfeldzone" is both confusing and inaccurate, and it is proposed to substitute for it the term "scurvy line."

5. Scurvy can be diagnosed by the roentgenogram before any of the accepted clinical symptoms (pain, hemorrhagic manifestations) have appeared.

AMOUNT OF CEREBROSPINAL FLUID IN HYDROCEPHALUS

METHOD FOR ESTIMATION AND ITS CLINICAL APPLICATION *

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AND
MENDEL ZELIGS, M.D.
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It is difficult to measure the progress of hydrocephalus. The method of estimating changes in the amount of cerebrospinal fluid by the effect produced on the size of the head is unsatisfactory, the variations in circumference showing only relatively gross changes and not giving any definite idea of the actual amount of fluid present in the cranium. The thickness of the brain tissue in the region of the parietal lobes can be gaged roughly by noting the distance it is necessary to insert a needle before the ventricles are entered, but this procedure again furnishes no information on which to base an estimate of the actual amount of fluid in the ventricles and subarachnoid space.

A knowledge of the quantity of cerebrospinal fluid in hydrocephalus would certainly be advantageous. It could be used as an index of the progress of the disease, and a variation in the amount would probably denote any change in the condition more quickly than would an increase or decrease in the external circumference of the head or a variation in the thickness of the cerebral cortex.

METHOD

Before proceeding to the method of estimating the amount of cerebrospinal fluid, it is first necessary to determine the type of hydrocephalus in the manner described by Dandy and Blackfan.[1] Briefly, this consists in injecting neutral phenolsulphonephthalein into the ventricles, the dye appearing within three minutes in the fluid obtained by lumbar puncture if no obstruction is offered to the flow of fluid from the ventricles into the subarachnoid space, that is, if obstructive hydrocephalus is not present. If a known amount of phenolsulphonephthalein is injected into the spinal canal (or into the ventricles in the absence of obstructive hydro-

* Received for publication, May 9, 1925.

* From the B. K. Rachford Department of Pediatrics, University of Cincinnati.

* Read before the American Pediatric Society, Washington, D. C., May 4, 1925.

1. Dandy, W. E., and Blackfan, K. D.: Internal Hydrocephalus. An Experimental, Clinical and Pathological Study, Am. J. Dis. Child. **8**:406 (Dec.) 1914.

cephalus), and the excretion of the dye in the urine is estimated, the presence and degree of communicating hydrocephalus can be determined. After ventricular injection, the dye should normally appear in the urine in from ten to twelve minutes; during two hours, from 12 to 20 per cent. of it should be excreted. After injection into the spinal subarachnoid space it should appear in the urine in from six to eight minutes, from 35 to 60 per cent. being excreted in two hours.

The following method suggested by one of us (M.Z.) is used to determine the amount of fluid in the ventricles in obstructive hydrocephalus. One cubic centimeter of neutral phenolsulphonephthalein is injected into the ventricle with an accurate syringe which is washed clean of the dye by withdrawing and reinjecting ventricular fluid several times before the needle is removed. The head is then elevated and lowered several times and rotated from side to side to facilitate admixture of the dye with ventricular fluid. In fifteen minutes some of the fluid is removed from the ventricle and the percentage of dye in this is determined by the usual colorimetric method employed in doing kidney function tests. The total amount of cerebrospinal fluid present in the ventricles can then be estimated. Thus, if 1 c.c. of fluid contains 1 per cent. of the dye, it will take 100 c.c. to contain 100 per cent. of it, or if 100 c.c. contains 10 per cent. it will take 1,000 c.c. to contain 100 per cent. In actual practice some of the ventriclular fluid may be alkalinized and diluted either one or more times so that a reading of from 75 to 100 per cent. is obtained. The following formula may then be used:

$$\frac{100{,}000}{\text{Reading} \times \text{Dilution}} = \text{Volume of fluid in c.c.}$$

If it previously has been determined that the condition is one of communicating hydrocephalus, it is necessary to know the amount of phenolsulphonephthalein which has been excreted in the urine, as this will give the amount which has left the cerebrospinal system. If a period of fifteen minutes is allowed for the appearance of the dye in the urine, the amount excreted in the next fifteen minutes should be known. In other words, the percentage of phenolsulphonephthalein excretion in the urine at the end of thirty minutes after its injection into the ventricle should be determined and allowance made for this. For example: 10 c.c. of fluid is withdrawn from the ventricle fifteen minutes after the injection into it of 1 c.c. of neutral phenolsulphonephthalein. This is alkalinized with sodium hydroxid and is diluted to 50 c.c. with water. A reading of 75 is obtained in the colorimeter. Then, by following the formula previously given ($\frac{100{,}000}{75 \times 5}$), the figure 266 is obtained. The urinary excretion of phenolsulphonephthalein thirty minutes follow-

ing its injection into the ventricle is 2 per cent. Therefore 5 (2 per cent. of 266) should be deducted from 266 and the figure 261 is obtained, which represents the total amount of fluid in cubic centimeters in the ventricles and in the subarachnoid space.

The error in estimating the amount of fluid in the ventricles in obstructive hydrocephalus would be that common to all colorimetric methods, provided that thorough admixture of the dye with ventricular fluid had occurred. It is obvious that the amount of phenolsulphonephthalein injected must be measured accurately. In communicating hydrocephalus, the arbitrary time in which the urinary output of phenolsulphonephthalein is determined may introduce a slight error, but in any event this will be inconsiderable. Error will also occur if some of the cerebrospinal fluid has been blocked off from the general system by adhesions.

CASE REPORT

D. S., a boy, colored, aged 8 weeks, was admitted to the Pediatric Service of the Cincinnati General Hospital, on Oct. 8, 1924. The family history had little significance; syphilis was denied and the history did not suggest it. Although tuberculosis had been present in the mother's family the patient had not been exposed to it. During pregnancy the mother suffered from vague joint pains but otherwise was not ill. Labor had been difficult and noninstrumental, and at birth the infant's scalp was swollen and his eyes closed. This swelling was apparently due to edema as it disappeared after three days. When the infant was 1 week of age, the mother noticed that his head began to increase in size, this becoming increasingly more evident. The child had been artificially fed since birth. The stools were loose and frequent and the patient vomited two or three times a day, but not in a projectile manner.

The physical examination revealed a fairly well nourished infant. The circumference of the head was 51.25 cm. The anterior fontanel was large, tense and bulging; the sutures were widely separated and the forehead was quite prominent. The eyes were rotated downward showing the sclera above and there was external strabismus of the left eye. The fundi were normal. The physical examination otherwise was essentially negative. There was no external or roentgen-ray evidence of spina bifida. Intracutaneous tuberculin reactions were negative. A low-grade fever was present on admission and at irregular intervals thereafter.

October 10 (two days after admission), 1 c.c. of neutral phenolsulphonephthalein was injected into the right lateral ventricle. Twenty minutes later a cisterna puncture was made and clear fluid was obtained. On examination of the ventricular fluid it was found to be clear but globulin and 106 cells, chiefly polymorphonuclears, were present, and it did not reduce Fehling's solution. The Wassermann reaction performed on this fluid was negative as was the Wassermann reaction on the blood. The bacteriologic examination made by Dr. W. B. Wherry, demonstrated intracellular and extracellular staphylococci on direct smear and these organisms were found by cultural methods.

Repeated ventricular punctures were done for the relief of pressure. October 16 (eight days after admission) the circumference of the head had decreased to 48.5 cm. An estimation of the amount of cerebrospinal fluid in the ventricles (according to the method previously outlined) gave the figure 575 c.c. The urine excreted in the twenty-four hours following phenolsulphonephthalein injection into the ventricle contained only 5 per cent. of the dye. Bacteriologic study of the ventricular fluid at this time by Dr. Wherry showed that the staphylococci had diminished in number and many more of them were intracellular than on the previous examination.

November 10 (33 days after admission) the circumference of the head was 47.75 cm. The child's general condition had improved. One cubic centimeter of neutral phenolsulphonephthalein was again injected into the right lateral ventricle. When cisterna puncture was performed twenty minutes later, the dye was not only present in the fluid contained but when compared colorimetrically with the ventricular fluid it was found to be in equal concentration in both. Further evidence of a presumptive nature of the free communication between ventricles and cisterna was furnished by comparing the cell counts, 212 cells being present in the ventricular fluid and 203 in the cisterna fluid. The urine collected at this time showed 2 per cent. of the dye in two hours and 22 per cent. in twenty-four hours. The estimated amount of cerebrospinal fluid at this time was 560 c.c. That the delay in urinary excretion of phenolsulphonephthalein was not due to faulty kidney function was later determined, a urinary output of 51 per cent. being obtained in the two hours following intramuscular injection.

November 25 (forty-eight days after admission), the cerebrospinal fluid obtained by spinal puncture was sterile. The circumference of the head at this time was 48 cm. and it remained at about this figure until December 18 (seventy-one days after admission) when it suddenly began to increase, reaching its greatest circumference of 52.25 cm. in a few days. When ventricular puncture was performed on December 19 (seventy-two days after admission), 255 c.c. of fluid under markedly increased pressure was removed. This contained 38 cells to the cubic millimeter, gave a 2+ globulin reaction but on culture proved to be sterile. Phenolsulphonephthalein injected into the ventricle at this time failed to appear in the fluid obtained at lumbar puncture. The estimated amount of fluid in the ventricles was 1,110 c.c. on December 22 (seventy-five days after admission), at which time the circumference of the head was 52.25 cm.

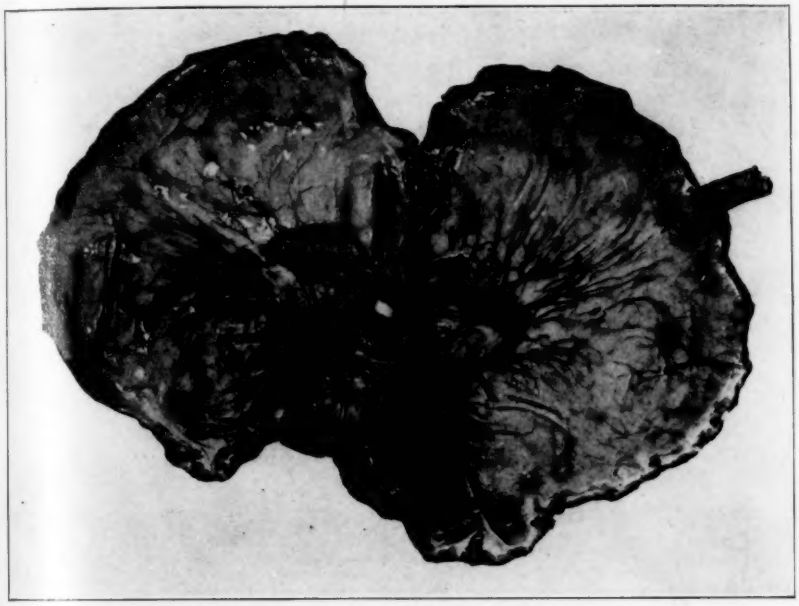
The child then developed attacks of projectile vomiting and dyspnea, these symptoms being temporarily relieved by frequent ventricular punctures with the removal of about 200 c.c. of fluid on each occasion. December 24 (seventy-seven days after admission), the patient developed pneumonia and death followed in less than forty-eight hours. The circumference of the head after death was 50.5 cm.

Treatment.—In addition to the repeated ventricular punctures, other methods of treatment were carried out. An autogenous vaccine prepared by Dr. Wherry from the staphylococcus obtained from the ventricular fluid was daily injected intracutaneously from October 16 (eight days after admission) to November 17 (forty days after admission). During this period, 2 intraventricular injections of 10 c.c. each of normal human serum were given and 1 injection of 10 c.c. of the patient's own serum—the last injection after twenty days of vaccine treatment. Normal human serum often contains opsonins for the staphylococcus. It was also hoped that vaccine treatment had stimulated the formation of these substances in the patient's own blood. Following the suggestion of Marriott,[2] theobromin sodio salicylate (diuretin) was given in doses varying from 12 to 20 grains a day. This drug was administered during several periods, both during the stage when the hydrocephalus was obstructive in type and later when this was relieved and communicating hydrocephalus existed.

Necropsy.—This was performed by Dr. J. Ganim. The examination was confined to the brain and spinal cord. The circumference of the head was 50.55 cm. By aspiration, 740 c.c. of thin, turbid, blood tinged fluid was removed from the ventricles and 120 c.c. of thin, slightly turbid, yellowish fluid from the region of the cisterna magna. On removal, the brain weighed 675 gm. The cerebral convolutions were flattened and the cerebral cortex was thin, measuring in some places only 5 mm. The meninges at the base of the brain were cloudy and moderately thickened but on the cortex, little gross pathologic change was present. When opened, the lateral ventricles were found to be dilated tremendously. The

2. Marriott, W. McK.: The Use of Theobromin Sodio Salicylate (Diuretin) in the Treatment of Hydrocephalus, Am. J. Dis. Child. **28**:479 (Oct.) 1924.

choroid plexuses stood out as firm dull cords which were tightly adherent to the wall of the ventricles. The third and fourth ventricles were normal in size. The aqueduct of Sylvius was not demonstrated, although the appearance of the dye in the cisterna fluid after ventricular injection during life proved that this passage was not congenitally obstructed. On the superior surface of the left cerebellar hemisphere was an irregular, somewhat circular, puckered scar, measuring 3.5 cm. in diameter. The greatest depth of this scar was 5 mm. and it did not appear to extend into the substance of the cerebellum. Microscopic examination of the brain and meninges demonstrated that the pathologic process was confined to the latter.



The brain, showing the tremendously dilated lateral ventricles and the scar on the superior surface of the left cerebellar hemisphere.

COMMENT

The condition presented several features of interest. It proved to be hydrocephalus due to exudate caused by a staphylococcus which was evidently of low virulence. In the beginning the failure to obtain phenolsulphonephthalein by cisterna puncture after its injection into the ventricle demonstrated that the hydrocephalus was of the obstructive variety. Later, perhaps due to treatment by vaccine and serum, the obstruction to flow from the ventricles was relieved. It was possible to determine this change by the appearance of phenolsulphonephthalein in the cisterna fluid after its injection into the ventricles, and also to show that communication of the ventricles with the cisterna was free by the equal concentration of dye and by the similarity in the cell counts in

the fluids from both of these places. That communicating hydrocephalus then remained was proved by the delayed excretion of dye after ventricular injection.

The origin of the infection and whether it began in intra-uterine or extra-uterine life can only be surmised. The improvement in the symptoms, the decrease in the size of the head, the disappearance of organisms from the spinal fluid and the relief of obstruction to the flow of fluid from the ventricles for a time gave hope that cure might take place.

The institution of theobromin sodio salicylate (diuretin) medication probably had no effect in the early stage when obstructive hydrocephalus was present. According to Marriott, this drug raises the surface tension of the blood, a condition which tends to cause the passage of fluid from serous cavities and intracellular spaces into the blood. Because of the small amount of absorption occurring in the ventricles, it would be only in the communicating type of hydrocephalus that benefit could be expected from the use of theobromin sodio salicylate. Although it was also employed in our case at intervals during the stage when obstructive hydrocephalus had been relieved, no marked effect could be determined on the amount of urine excreted or on the specific gravity of the blood.

Circumference of Head and Amount of Fluid

Date, 1924	Circumference of Head	Amount of Fluid in Ventricles	Total Amount of Fluid in Ventricles and Subarachnoid Space	Remarks
Oct. 16	48.5 cm.	575 c.c.	.....	Obstructive hydrocephalus
Nov. 10	47.75 cm.	.....	560 c.c.	Communicating hydrocephalus
Dec. 22	52.25 cm.	1,110 c.c.	.....	Obstructive hydrocephalus
Dec. 26	50.5 cm.	740 c.c.	860 c.c.	After death

The estimated amount of cerebrospinal fluid proved to be of assistance in judging the course of the case. The amount of fluid estimated during life was not inconsistent with that found at necropsy. This may best be illustrated by the table.

CONCLUSIONS

A colorimetric method for estimating the amount of cerebrospinal fluid is presented. This method proved useful in judging the progress of a case of hydrocephalus. The case itself was of interest in that the hydrocephalus was due to the exudate caused by a staphylococcus.

RICKETS IN INFANTS

TREATMENT WITH IRRADIATED MILK *

BENJAMIN KRAMER, M.D.

BALTIMORE

About one year ago, Alfred F. Hess reported the interesting observation that when cotton and linseed oils are irradiated with the mercury vapor quartz lamp and then fed to rats along with a rickets-producing diet, they tend to prevent the development of rickets. More recently, Hess and Weinstock claim to have obtained similar results with a number of chemical substances, especially with cholesterol and phytosterol. Steenbock and his associates state that "growth promoting" and "calcium depositing properties" may be imparted to a large number of chemical substances by irradiation. All of these studies were made on animals. It is well known that cow's milk has practically no power to cure rickets in children. It seemed interesting, therefore, to determine whether sufficient antirachitic power to bring about actual cure of rickets in children can be imparted to milk by irradiation.

TREATMENT AND DIET

Eight children suffering from active, and in most instances severe, rickets were selected and treated in the hospital. Their ages ranged from 5 to 39 months, the majority being less than 2 years of age. The diet consisted of irradiated milk, orange juice and a cereal. The quantity of milk required for twenty-four hours was poured into a large shallow dish and was irradiated at a distance of 2 feet for not more than two hours.[1]

The treatment imparts a peculiar taste to the milk, but, in spite of this, little difficulty was experienced in having the children take the food. With one exception, all the children gained weight during the period of irradiated milk feeding.

DIAGNOSIS

The clinical diagnosis of rickets was confirmed by roentgenograms of the extremities, and by analyses of the calcium and inorganic phosphorus of the serum. After the necessary data had been obtained, the

* Received for publication, May 9, 1925.

* Read before the American Pediatric Society, Washington, D. C., May, 1925.

1. We are now convinced that the time of exposure was unnecessarily long and that equally good results may be obtained with a much shorter exposure, probably from ten to twenty minutes.

irradiated milk diet was begun. This was continued until definite signs of healing appeared in the roentgenograms of the extremities and the concentration of calcium and inorganic phosphorus in the serum had risen approximately to the normal level. The results are summarized in Table 1. In every instance the roentgenogram taken before treatment

TABLE 1.—*The Effect of Irradiated Milk Feeding on the Blood and Bones of Rachitic Children*

Name	Age	Date	Calcium in Mg. per 100 C.c. Serum	Inorganic Phosphorus in Mg. per 100 C.c. Serum	Product	Roentgenogram	Began Irradiated Milk Feeding
G.	13 mo.	10/ 6/24	9.2	3.3	30	Rickets.....	10/14/24
		10/27/24	10.0	4.6	46	Healing rickets	
		11/ 4/24	10.5	5.3	56	Healed rickets	
T.	17 mo.	10/24/24	10.0	3.2	32	Rickets.....	10/24/24
		11/ 4/24	10.4	6.0	62	Healing rickets	
S.	1 yr.	12/ 4/24	6.6	4.8	32	Mild rickets.....	11/25/24
		12/13/24	8.4	6.4	54		
		12/19/24	....	...	..	Definite healing	
E.	9 mo.	1/19/25	9.8	2.3	23	Severe rickets.....	1/21/25
		1/27/25	9.5	3.0	28		
		2/ 7/25	9.5	4.0	38	Definite healing	
		2/14/25	10.6	5.9	63	Rickets (almost completely healed)	
E.	3 yr., 3 mo.	1/13/25	....	...	..	Severe rickets.....	1/21/25
		1/19/25	9.7	2.7	26		
		2/ 7/25	10.2	5.4	55	Healing rickets	
		2/12/25	10.0	5.5	55	Well advanced healing	
C.	13 mo.	2/12/25	9.8	2.4	23	Severe rickets.....	2/21/25
		3/ 8/25	9.3	3.2	30	No change	
		3/14/25	10.0	3.5	35	Definite healing	
			3.21	10.2	42	Rickets almost healed	
R.	9 mo.	2/ 9/25	9.8	2.6	25	Severe rickets.....	2/10/25
		3/ 8/25	9.0	4.2	38	Definite healing	
		3/21/25	9.6	4.3	42	Well marked healing	
K.	6 mo.	2/16/25	7.4	3.2	24	Severe rickets.....	2/21/25
		3/ 8/25	8.8	5.9	52	Beginning healing	
		3/14/25	8.6	6.1	52	Marked healing	
		Patients Treated by Ineffective Method but on Same Diet with Unirradiated Milk					
B.	5 mo.	2/ 7/25	9.3	2.6	24	Severe rickets	
		2/21/25	9.0	1.9	17	Severe rickets	
		3/ 8/25	8.8	3.0	26	Severe rickets	
C.	8 mo.	3/ 8/25	8.8	3.0	26	Severe rickets	
		3/21/25	7.4	3.0	22	Severe rickets	
		3/31/25	7.8	3.8	30	Severe rickets	
		4/ 3/25	....	3.8	..	Severe rickets	

showed rickets to be present. Five of the patients were suffering from a severe form of the disease. Of the eight children, six had an approximately normal calcium concentration in the serum and a low inorganic phosphorus. One was suffering from active and another from latent tetany. The product of the concentrations of the inorganic phosphorus and the calcium expressed in milligrams per hundred cubic centimeters of the serum was about thirty in every instance (Figs. 1 and 2).

Following irradiated milk feeding, the level of inorganic phosphorus increased in the serum and in four weeks it had reached approximately the normal level. In every instance the roentgenogram showed early

but definite signs of healing by the end of the third week, which was well marked or complete at the end of the fourth week. The older children responded more rapidly to treatment.

CALCIUM AND PHOSPHORUS BALANCE

Studies of the calcium and the phosphorus balance were made on two children during a preliminary four-day period and after the children had received irradiated milk for at least two weeks. As shown in

Fig. 1.—Roentgenogram of wrist before and four weeks after feeding irradiated milk, showing increased length of radius and ulna due to fresh deposition of lime salts; also appearance of centers of ossification at lower end of ulna and in carpal bones.

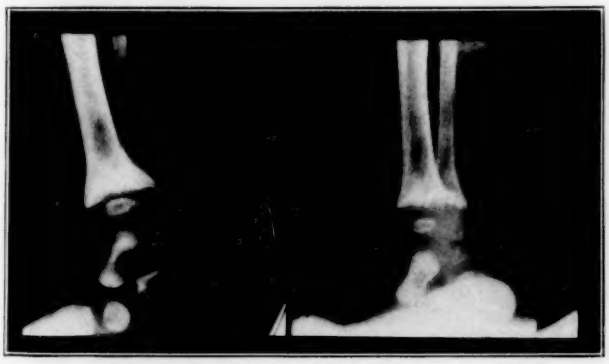


Fig. 2.—Roentgenogram of lower extremity of same child before and four weeks after feeding irradiated milk. Changes similar to those seen at wrists.

Table 2, in each instance there was a marked increase in the retention of calcium and phosphorus during the period when irradiated milk was fed. Concurrently with the before-mentioned children, two patients who were treated by another method failed to show any improvement at the end of four weeks of treatment, although fed on the same diet, using milk which had not been irradiated.

TABLE 2.—*Calcium and Phosphorus Balance Before and After Feeding Irradiated Milk*

			Intake	Urine	Stool	Total Output	Retention	Per Cent. Retained
W. K., 6 mo.*	Calcium	Before	4.22	0.03	3.46	3.49	0.73	17.3
		After	4.99	0.02	1.91	1.94	3.05	61.0
	Phosphorus	Before	3.69	1.04	1.62	2.66	1.03	28.0
		After	4.52	1.72	0.56	2.29	2.23	40.0
L. C., 13 mo.†	Calcium	Before	4.60	0.02	4.0	4.02	0.58	12.6
		After	5.27	0.02	3.4	3.42	1.85	35.3
	Phosphorus	Before	4.03	1.56	1.60	3.16	0.87	21.0
		After	4.61	2.33	0.68	3.01	1.60	35.0

	Before	After
* Calcium in 100 c.c. serum	7.4	8.8
Inorganic phosphorus in 100 c.c. serum	3.2	5.9
	Before	**After**
† Calcium in 100 c.c. serum	9.8	9.6
Inorganic phosphorus in 100 c.c. serum	2.4	3.5

CONCLUSIONS

1. In a series of eight patients with active rickets, the administration of irradiated milk produced healing in every case. This was demonstrable at the end of the third week and was marked at the end of the fourth week.

2. The chemical changes in the blood following this treatment were identical with those previously reported, which followed the administration of cod liver oil to rachitic children or the exposure of such children to ultraviolet rays or to sunlight.

3. Irradiated milk feeding induces a marked retention of both calcium and phosphorus.[2]

2. The figures are reproductions of the roentgenograms of the upper and lower extremities of one child taken before and four weeks after treatment with irradiated milk. The changes are identical with those following the administration of cod liver oil.

SOME SPECTROSCOPIC OBSERVATIONS ON COD LIVER OIL*

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As a preliminary step in the investigation of the relationship between cod liver oil and ultraviolet radiation as antirachitic factors, the experiments of Kugelmass and McQuarrie [1] on the photoactivity of cod liver oil were repeated. In every case negative results were obtained.

METHOD

An apparatus similar to that described by these investigators was employed. Eastman's Speedway plates, possessing properties similar to Seed's Graflex 60, were used. Since these plates proved to be sensitive to the red light in the room, the whole experiment was carried out in total darkness. The cod liver oil was a sample of Mead and Johnson's, guaranteed as to vitamin activity. One sample was exposed after air had bubbled through it for about two minutes. In another sample, the apparatus was so arranged that a slow stream of dry oxygen was passed continuously over the surface of the oil during the exposure.

Under these conditions, a twenty-four and a sixty-six hour exposure to the oxidizing cod liver oil, made alkaline with 10 per cent. potassium hydroxid, produced no darkening of the photographic plate. A seven-day exposure to the oil, untreated by alkali, also produced no effect. These results gave no evidence that cod liver oil, while oxidizing, emits ultraviolet light. That oxidation of the oil plays no part in its action as an antirachitic factor would be expected from the findings of McCollum, Simmonds, Becker and Shipley,[2] that when air is bubbled through cod liver oil heater to 100 degrees for from ten to twenty hours, vitamin A is destroyed but the oil is still as effective as the untreated oil in curing rickets.

ANTIRACHITIC FACTOR

Just what the potent antirachitic factor of cod liver oil is, and what connection or relation it has to the physical or chemical influences of light, has been a subject of continued interest and considerable investigation.

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* Received for publication, May 13, 1925.

* From the Department of Pediatrics, University of Minnesota.

* Read before the American Pediatric Society, Washington, D. C., May, 1925.

1. Kugelmass, F. N., and McQuarrie, I.: Science **60**:272, 1924.

2. McCollum, E. V.; Simmonds, N.; Becker, and Shipley, P. G.: Bull. Johns Hopkins Hosp. **31**:221, 1922.

In 1921, Wacker and Beck [3] pointed out that, besides other chemically not well characterized substances, cholesterol played a significant rôle in determining the activity of the antirachitic fat-soluble A in cod liver oil.

About the same time, Zucker [4] found that the antirachitic substance of cod liver oil is found in the ether-soluble unsaponifiable fraction after alkaline hydrolysis. This substance is not an organic base of the type described as occurring in cod liver oil. The author also at that time did not believe that it was cholesterol.

He found that cholesterol crystallized from a solution of the unsaponifiable matter in alcohol was inactive. He concluded that the substance was possibly a sterol related to cholesterol or a cholesterol derivative.

In a later communication, Zucker [5] reports an antirachitic substance obtained from cod liver oil, which in dilutions as high as 1 : 1,000 was still as active as cod liver oil and was entirely free from fat-soluble vitamin A. This substance was prepared by extracting the oil with 95 per cent. alcohol, saponifying with sodium hydroxid, precipitating the calcium soap and active substance in an aqueous solution and extracting the precipitate with acetone.

Steenbock [6] found that from the standpoints of growth, calcification of bones and maintenance of normal calcium and phosphorus content of blood, the ether extract of saponified cod liver oil is as efficacious as the untreated oil.

FURTHER EXPERIMENTS

A large amount of excellent research has established beyond doubt the antirachitic property of the ultraviolet ray alone.

Hess [7] found that the curative antirachitic ray lay somewhere in the neighborhood of from 300 to 313 millimicrons.

Shipley [8] believed that the shorter ultraviolet rays about 210 millimicrons wave length have even greater antirachitic effect.

In a series of recent communications, Hess [9] and his co-workers and

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3. Wacker, L., and Beck, K. F.: Berl. Klin. Wchnschr. **18**:453, 1921.

4. Zucker, I.; Pappenheimer, A., and Barnett, M.: Proc. Soc. Exper. Biol. & Med. **19**:167, 1921.

5. Zucker, T.: Proc. Soc. Exper. Biol. & Med. **20**:136, 1922.

6. Steenbock, H.; Jones, J. H., and Hart, E. B.: J. Biol. Chem. **58**:303 (Dec.) 1923.

7. Hess, A., and Weinstock, M.: A Study of Light Waves in Their Relation to Rickets, J. A. M. A. **80**:687 (March 10) 1923.

8. Shipley, P. G.: Faulty Diet and Its Relation to the Structure of Bone, J. A. M. A. **79**:1563 (Nov. 4) 1922.

9. Hess, A.: Proc. Am. Pediat. Soc. **36**: 1924; Hess, A., and Weinstock, M.: Proc. Soc. Exper. Biol. & Med. **22**:5-6, 1924-1925.

Steenbock [10] and his co-workers have reported a remarkable series of experiments, in which they showed that antirachitic properties can be imparted to various inert fluids by means of ultraviolet irradiation.

Steenbock and Daniels [11] also found that prolonged or excessive irradiation can cause a loss of the antirachitic factor. This was true for cod liver oil and for other oils if irradiated for seventeen hours.

They found the antirachitic principle of nonirradiated and irradiated cod liver oil entirely stable to saponification.

THE ELEMENT IN COMMON

Since cod liver oil and ultraviolet radiations have been found to produce apparently the same effects in preventing rickets, it is of great interest to find out what, if any, common element there is between two such different factors. The work of Kugelmass and McQuarrie,[1] that cod liver oil and other antirachitic factors, when oxidized, give off ultraviolet radiations, has been disproved by our experiments. It seemed to us that there must be an intimate connection between cod liver oil and ultraviolet radiation, and that perhaps a key to the solution might be found by studying the absorption spectrum of cod liver oil and comparing it with that of cottonseed oil, which has no antirachitic properties. When a substance exhibits a characteristic absorption band, it means that it can absorb energy of definite wave lengths and this energy may be stored up and either given out again or used up in some way. The effect of the energy given out by the cod liver oil might then be similar to the effect of the energy of the ultraviolet radiation. If the cod liver oil showed an absorption spectrum characteristically different from that of cottonseed oil, and especially if the wave lengths absorbed corresponded to the wave lengths of the ultraviolet which are effective in curing rickets, this would be strong support for such a theory.

The absorption spectrum of cod liver oil did show some indications of two shallow absorption bands, heading about 328 and 279 millimicrons, while that of cottonseed oil showed only general absorption. The absorption spectrum also showed that cod liver oil had a greater capacity for absorbing ultraviolet radiations than cottonseed oil. A layer 1.5 mm. thick of the cod liver oil absorbed all of the ultraviolet rays beyond 377 millimicrons, or practically all of the radiations. In thick enough layers, cottonseed oil absorbed practically as much of the ultraviolet, but these layers were at least twenty-four times as thick as those of cod liver oil.

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10. Steenbock, H.: Science **60**:224, 1924; Steenbock, H., and Nelson, M. T.: J. Biol. Chem. **62**:209 (Nov.) 1924.

11. Steenbock, H., and Daniels, A.: Irradiated Foods and Irradiated Organic Compounds: Therapeutic Possibilities, J. A. M. A. **84**:1093 (April 11) 1925.

Since the cod liver oil is a mixture containing much fat and small proportions of other substances, and since the shallow bands in its absorption spectrum might be due to an active substance the absorption of which might be masked by dilution by the oil, it was thought advisable to separate the unsaponifiable fraction, which has been found by several investigators to be antirachitic. Three and three-tenths grams of unsaponifiable fraction, a cream-colored, semisolid substance (partially crystalline, but apparently mixed with an oily substance), was isolated out of 890 gm. of oil. Such a substance, being opaque, had to be put into solution before its absorption spectrum could be taken. Absolute alcohol was used. For purposes of comparison, then, it was necessary to have also an absorption spectrum of cod liver oil in alcohol solution. Since the unsaponifiable fraction contained a great deal of cholesterol (66.8 per cent. as determined by digitonin precipitation), and since it was best for our purpose to eliminate as many of its inactive ingredients as possible from the mixture, the cholesterol was removed as completely as possible from the unsaponifiable fraction by crystallization from alcohol solution. This left a yellow, viscous, oily residue which, according to Zucker,[12] is still active in preventing rickets. The absorption spectrum of this viscous residue in alcohol solution was also taken. In each case a 2 per cent. solution was used. The results are shown in Chart 1. A study of the graph shows that the unsaponifiable fraction has a much greater power of absorbing ultraviolet radiation than the whole cod liver oil, and that after the cholesterol is removed, it absorbs more than ever, probably a dilution effect. (According to Beer's law, the light absorbing power of a solution is proportional to the concentration of the absorbing substance.) The shallow bands in the cod liver oil have appeared again in the absorption spectrum of its alcohol solution and in the same position, but they have entirely disappeared from that of the unsaponifiable fraction, whether it contains the cholesterol or not. There is simply a large amount of general absorption, and this may be due to the antirachitic factor or to some other substance in the cod liver oil.

At this time the articles by Hess [13] and a report by Steenbock appeared, stating that cholesterol and phytosterol, when irradiated by ultraviolet light become antirachitic; also the statement by Hess that spectrograms of cholesterol after irradiation transmit more of the extreme ultraviolet than before. Since the latter statement was the reverse of what we would have predicted from our spectrographic results

12. Zucker, T.; Pappenheimer, and Barnett, M.: Proc. Soc. Exper. Biol. & Med. **19**:168, 1921-1922.

13. Hess, A.; Weinstock, M., and Helman, F. D.: J. Biol. Chem. **63**:305, 1925.

as far as we had gone, it seemed desirable to repeat this work of Hess on the absorption spectrum before and after irradiation.

Pfanstiehl's chemically pure cholesterol was found to melt at 143 degrees, but after two recrystallizations, it melted at 148.5 degrees, the correct melting point of cholesterol. Evaporation of the mother liquor gave a product melting at 148.1 degrees, showing the high purity of our sample. Absorption spectra of this cholesterol in 1 and 2 per cent. solutions in absolute alcohol showed that absorption due to effects of

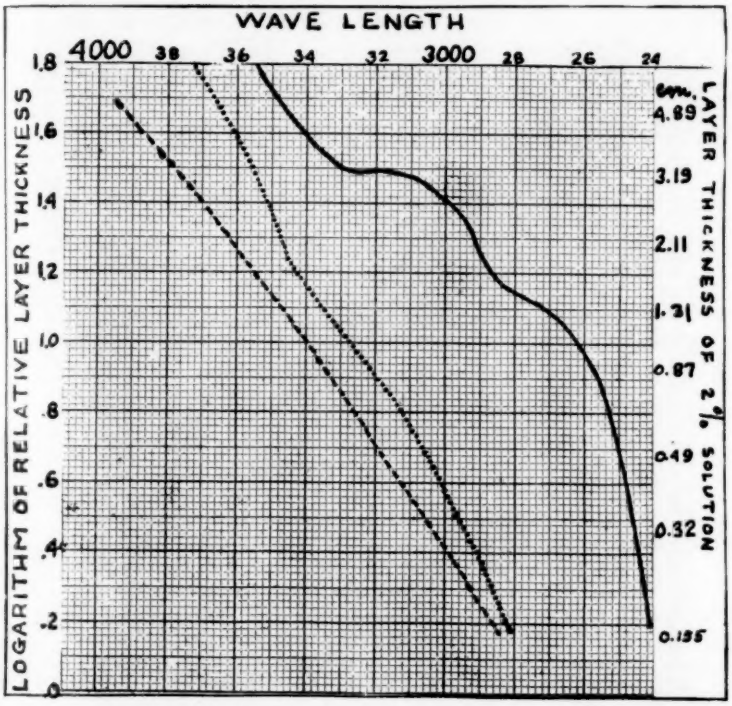

Fig. 1.—Results of absorption spectrum. Plain line, cod liver oil; dotted line, unsaponifiable fraction; broken line, unsaponifiable fraction with cholesterol removed.

the alcohol concealed the effects due to the cholesterol. This solvent was then discarded and ether, dried over calcium chlorid and distilled, was used. Ether so treated is much more transparent in the shorter wave lengths of the ultraviolet. This proved satisfactory. A 2 per cent. solution of cholesterol showed little general absorption up to layers of 4.2 cm., although two faint absorption bands were visible. A 4 per cent. solution and layer thicknesses up to 9.1 cm. gave better results, that is, more definite absorption bands, heading at 295 and 281 millimicrons, and more general absorption in the thicker layers.

The ether solution of the cholesterol was irradiated by a quartz mercury vapor arc, one sample for five minutes, another for ten, and still another for twenty minutes, made up to the same concentration again and their absorption spectra taken. All three showed the same effect. This agrees with the finding by Hess that linseed oil irradiated for two minutes acquired antirachitic properties. Their spectra showed no sign of the characteristic absorption bands of cholesterol, but a greater amount of general absorption. A comparison of the absorption spectra

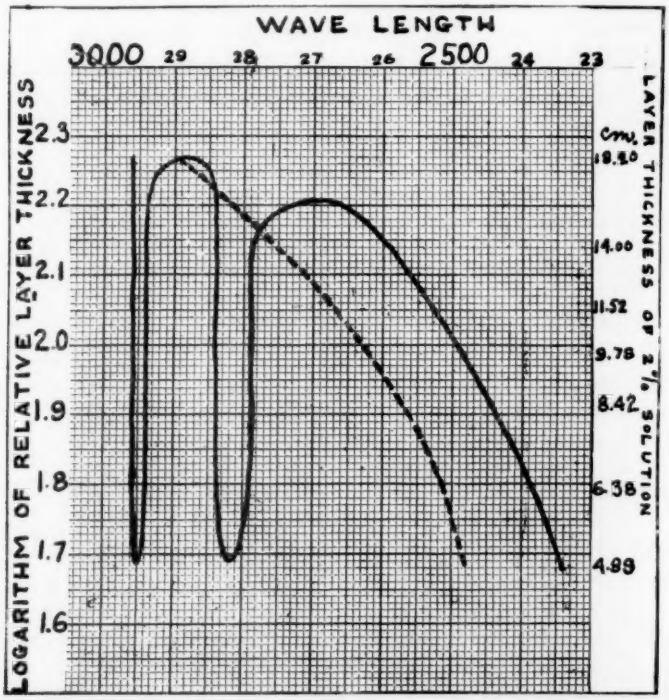

Fig. 2.—A comparison of the absorption spectra of cholesterol before and after irradiation. Plain line, cholesterol before irradiation; broken line, cholesterol after irradiation.

of cholesterol before and after irradiation may be made from Chart 2. Our results do not agree with the findings of Hess that the irradiated cholesterol transmits more of the ultraviolet, for in every case general absorption in the irradiated cholesterol cuts off more of the ultraviolet than in the cholesterol which has not been irradiated, that is, the spectrum through corresponding layer thicknesses was visible farther out toward the short wave lengths of the ultraviolet in the case of the nonirradiated cholesterol. However, it is possible that Hess was referring to the region in which selective absorption takes place in the

cholesterol. In that region it is true that the irradiated cholesterol transmits more, but that region could hardly be called the extreme ultraviolet.

The curves shown by the graph are drawn by plotting the limits of absorption against the logarithm of the layer thickness. The determination of the limit of absorption presents difficulties, since the personal element enters in largely. Such a representation, also, cannot show with certainty whether the decrease in intensity, due to general absorption, is slow or rapid. To obviate such difficulties two of the absorption spectra, representing absorptions through equal layer thicknesses of the cholesterol solution before and after irradiation were subjected to the action of a precision densitometer, which registered on sensitive paper a

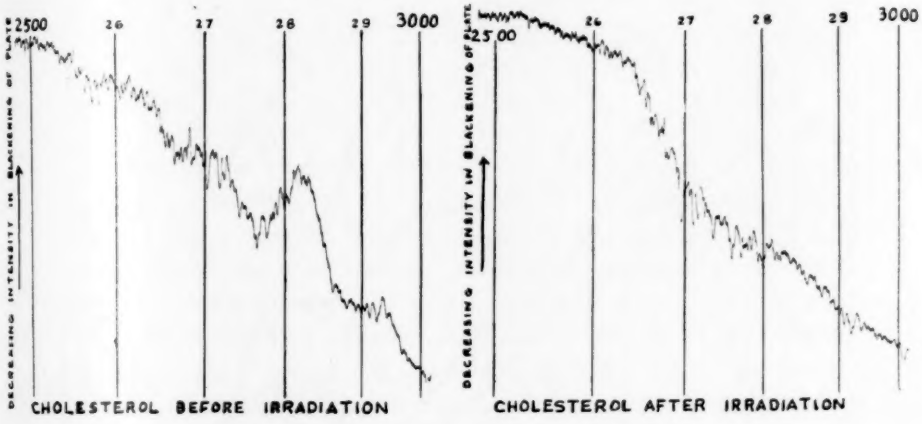

Fig. 3.—Curves before and after irradiation.

photograph of the relative intensities of that portion of the spectrum in which absorption was playing a part. Examination of the curve (Chart 3) for the cholesterol before irradiation shows two decided bands, or lightenings of the spectrum (indicated by a sudden rise in the curve followed by a drop). After this there is a gradual diminution in intensity with indications of two other bands which were not apparent in a visual examination of the spectrum. The curve for cholesterol after irradiation shows a complete change. There is no evidence whatsoever of any absorption bands, but the curve does show a sudden rise, indicating a sudden decrease in intensity or a sudden absorption in the spectrum, an effect which is lacking in the other curve.

The relation of the absorption of cholesterol to that of the cod liver oil and its unsaponifiable fraction may be seen from Chart 4, in which all the curves are drawn to the same scale and put into their relative positions. Examination of the graph shows that if the irradiated

cholesterol is the same substance as the antirachitic factor in cod liver oil, then it could not show up in the absorption spectrum of cod liver oil, for it is so little absorptive and its concentration is so small. The absorption of the oil and its unsaponifiable fraction obtained must then be due to some constituent of the oil other than the active factor. A problem still to be solved is whether the antirachitic substance in the cod liver oil is the same as that which is formed when cholesterol is irradiated.

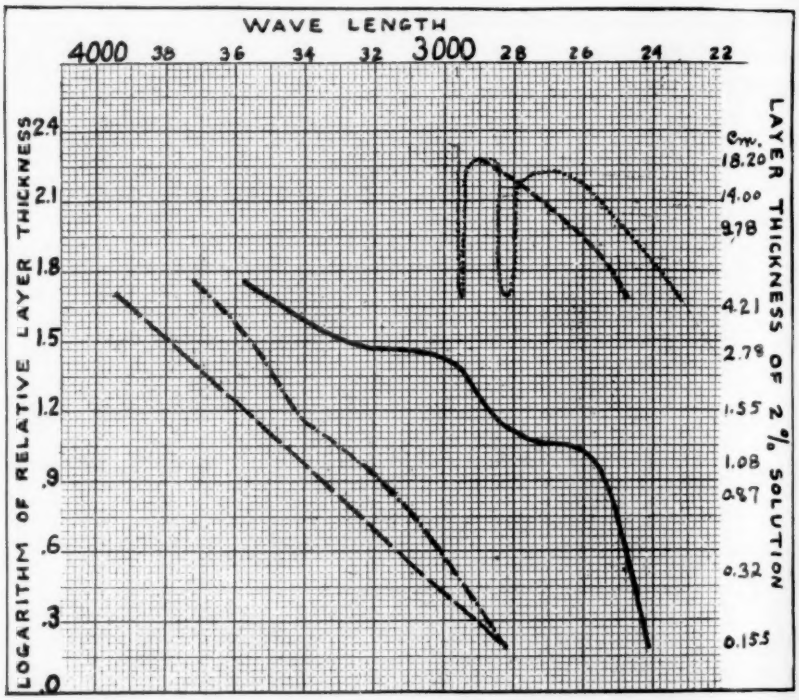

Fig. 4.—Relation of absorption of cholesterol to that of cod liver oil. Plain line, cod liver oil; dot and dash line, unsaponifiable fraction; broken line, unsaponifiable fraction, cholesterol removed; dotted line, cholesterol before irradiation; dash line, cholesterol after irradiation.

IRRADIATED CHOLESTEROL CHANGES

Another problem is what happens to the cholesterol when it is irradiated. Is it changed into another chemical substance, and if so, is only a small part of it changed, or is the whole of it changed?

Spectrographic evidence has shown that after irradiation for five minutes, the substance shows the same absorption spectrum as after irradiation for twenty minutes. It also shows that at least half of the cholesterol has been changed to some other form, if Beer's law holds,

for at layer thicknesses of 7 cm. there is not the slightest indication in the irradiated cholesterol of the bands which were quite evident in the nonirradiated form at a layer thickness of 3.2 cm. One other possibility should be kept in mind. The substance in which the absorption spectrum is changed may be a small amount of impurity in the cholesterol which is not removed by repeated crystallizations from alcohol, and which is exceedingly absorptive. In such a case this small amount might be completely transformed and the cholesterol remain unchanged.

The melting point of the cholesterol before and after irradiation also gives evidence of a change, for on evaporation of the ether from two irradiated samples which originally melted at 148.5 degrees, the residue melted at 143 degrees. Similar treatment with a nonirradiated sample gave an unchanged melting point of 148.5 degrees. However, recrystallizing the irradiated ether residue from alcohol resulted in a large crop of cholesterol melting at 148.5 degrees, therefore unchanged cholesterol. A small residue was left on evaporation of the mother liquor, which apparently contained more cholesterol but had a brownish color. This residue started to gum together at 135 degrees. This evidence seems to show that only a small amount of the cholesterol has been chemically changed, unless solution in the hot alcohol has reconverted it to its original form. It seems reasonable to correlate all of these facts by the supposition that the whole of the cholesterol is converted by irradiation into a different, more active form which is unstable and which is destroyed by evaporation of the solvent, or by solution in alcohol. The lowering of the melting point may be explained by the formation of another product through a secondary reaction, a supposition which is borne out by the fact that Steenbock has shown that prolonged irradiation of cholesterol destroys its antirachitic activity entirely.

At this point it might be well to raise the question whether the active substance in cod liver oil is identical with the activated cholesterol. Aside from the problem of how the cholesterol in the fish became activated, the difference in the stability of the two causes a difficulty in correlating them. The active factor in cod liver oil is reported as being very stable, resistant to boiling with concentrated alcoholic alkali during saponification and still stable during the process of crystallizing out the cholesterol. On the other hand, the activated cholesterol material (as we have seen), apparently is converted to inactive cholesterol by the simple process of evaporating the ether and recrystallizing from alcohol.

WAVE LENGTHS

Another interesting question raised by our results deals with the wave lengths which are absorbed by the cholesterol and by the active

material. Our absorption spectra show that those wave lengths between 294 and 296 millimicrons and between 279 and 294 millimicrons are selectively absorbed by the nonirradiated cholesterol, and beyond 294 millimicrons a great deal of general absorption takes place. It is reasonable to expect that the wave lengths which are selectively absorbed and which disappear on irradiation are those wave lengths which are effective in activating the cholesterol. It is a fundamental law of photochemistry that only absorbed light is photochemically active.

The photometric curve shows that a wave length of 302 millimicrons (that found by Hess), to be antirachitic in its effect, is just at the point where a fairly rapid absorption begins. There is some question whether it should be included in the selective absorption of the first band. If it is, then all evidence agrees with the supposition that ultraviolet light brings about its antirachitic effect by converting the cholesterol to an active substance, which, by some ordinary chemical reaction or by catalysis, brings about a proper calcium metabolism in the body. If this wave length of 302 millimicrons cannot be included in the selective absorption, it means either that activation of the cholesterol is brought about by a general absorption of ultraviolet radiation of wave lengths shorter and including 302 millimicrons, or that the selective absorption converts the cholesterol into an active substance which in turn gives off energy in the form of an ultraviolet radiation of a wave length of 302 millimicrons. This question cannot be settled by the facts so far known. It would be interesting to find a filter which would absorb the radiations from 305 to 270 millimicrons, in order to see definitely whether activation in a biologic sense, or destruction of the bands, or both, could be produced by ultraviolet light of other wave lengths. This experiment will be attempted in the near future.

COMMENT

A suggestion which is offered as a result of our investigation is that in a further study of the activation of cholesterol, the disappearance of the bands in its absorption spectrum may be used as an index of its antirachitic activity, perhaps eliminating to some degree the necessity for rat experiments. Such an index probably could only apply to a pure substance, and, in any event, further data would be required before its efficiency could be assured.

As a result of our work, a great many questions have been raised, some of which may be difficult to settle. Further work on the subject is in progress. As the next step, we propose to investigate the time

rate of the reaction brought about by the irradiation of cholesterol by portraying photometrically the gradual disappearance of the characteristic bands of cholesterol on increasing exposure to ultraviolet radiation.

SPASMOPHILIA

INORGANIC CONSTITUENTS OF BLOOD AND CEREBROSPINAL FLUID *

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AND
J. I. HARTMAN, M.D.
CLEVELAND

Recent investigations concerning the etiology of infantile tetany have resulted in one definite conclusion, namely, that the blood calcium is markedly reduced during the active stage. This was first suggested by the experiments of Sabbatini,[1] and was proved finally by the accurate estimations of Howland and Marriott.[2] Earlier investigations by MacCallum and Voegtlin [3] had shown a similar decrease in the calcium content of the blood in experimental parathyroid tetany in dogs. These results have been confirmed by the subsequent work of other authors, both in experimental tetany and in infantile tetany. Another fact generally conceded is that the inorganic phosphorus content of the blood is usually either normal or elevated.

The work presented here was carried out in order to determine whether a concomitant lowering of the calcium content occurred in the cerebrospinal fluid in infantile tetany and, also, to determine if there was an increase in the inorganic phosphorus content, and if any significant change in other inorganic elements had taken place.

Several investigators have made determinations of the calcium content of the brains in parathyroid tetany and in infantile tetany. The majority of them have found the calcium content lower than in normal controls, which finding might well lead one to believe that the calcium content of the cerebrospinal fluid would be lower than normal in infantile tetany. Thus, Quest [4] determined the calcium content in the brains of fetuses and infants of various ages. He found the content high in the brains of fetuses and infants a few months old. In three cases of spasmophilia, the calcium content was decreased. In two cases of general muscular hypertonia (described by Czerny and Moser in 1894), the calcium content was normal. Aschenheim [5] reported similar results

* Received for publication, May 6, 1925.

* From the Department of Pediatrics, Lakeside Hospital and Western Reserve University Medical School.

1. Sabbatini: Riv. sper. di freniat. **27**:946, 1901 (quoted after MacCallum and Voegtlin).
2. Howland, J., and Marriott, W. McK.: Quart. J. Med. **11**:289 (July) 1918.
3. MacCallum and Voegtlin: J. Exper. Med. **11**:118, 1909.
4. Quest: Jahrb. f. Kinderh. **61**:114, 1905.
5. Aschenheim: Monatschr. f. Kinderh. **9**:366, 1910.

in dogs with parathyroid tetany and in infants with spasmophilia. He also noted a change in the $\frac{Na + K}{Ca + Mg.}$ ratio. Weigert [6] found the calcium content lowered in the brain of a dog presenting symptoms similar to those of infantile tetany. He used a dog of the same litter for a control. MacCallum and Voegtlin [3] reported like results in the case of dogs with parathyroid tetany. Contrary findings were reported by Leopold and Reuss,[7] who found the calcium content of the brain in one case of spasmophilia slightly increased, and by Cooke,[8] who reported that the brains of dogs dying with parathyroid tetany contained a slightly greater amount of calcium than those of normal dogs.

Determinations of the inorganic elements in the cerebrospinal fluid have not been numerous; this is particularly true in relation to spasmophilia. From the available literature we give the following brief review in tabular form (Table 1). More attention has been given to the calcium and inorganic phosphorus content than to the other elements.

In comparing the different results in Table 1, we find good agreement, provided we make due allowance for the less exact chemical methods used by the earlier workers. No essential changes have been reported in the different diseases investigated except as follows: Cohen [9] found the inorganic phosphorus content somewhat increased in certain inflammatory diseases of the central nervous system, that is, 2.4 mg. per cent. in a case of tuberculous meningitis, which represented his highest result. Depisch and Richter-Quittner,[10] in their chemical examination of 167 normal and pathologic spinal fluids, found an absence of calcium in some cases and abnormally large amounts in others. Their estimations of other inorganic constituents, both of the blood and spinal fluid, likewise, gave widely varying results which are so inconsistent with well established standards that they are of no value for comparison. Nowicka [11] reported the content of sodium chlorid in sixty cases of tuberculous meningitis definitely lower than in normal cases, namely, from 510 to 680 mg. per hundred cubic centimeters as compared with the average normal value of 733 mg. per hundred cubic centimeters. In cases of meningitis due to other causes, the content was lower than normal but the change was not so marked as in tuberculous meningitis.

Little was found concerning the chemistry of the cerebrospinal fluid in spasmophilia. Critchley and O'Flynn [12] found only a trace of calcium in one case of active infantile tetany. In two cases of latent tetany,

6. Weigert: Monatschr. f. Kinderh. **5**:457, 1906.
7. Leopold and Reuss: Wien. klin. Wchnschr. 1243 (Aug. 27) 1908.
8. Cooke: J. Exper. Med. **12**:45 (Jan.) 1910.
9. Cohen: Quart. J. Med. **17**:289 (April) 1924.
10. Depisch, F., and Richter-Quittner, M.: Wien. Arch. f. inn. Med. **5**:321 (Jan.) 1923.
11. Nowicka: Arch. de méd. d. enf. **27**:726 (Dec.) 1924.
12. Critchley, M., and O'Flynn, E.: Brain **47**:337 (Aug.) 1924.

TABLE 1.—*Average Content of Inorganic Constituents Found in Cerebrospinal Fluid* *

Author	Calcium	Potassium	Sodium	Magnesium	Inorganic Phosphorus	Chlorin	Sodium Chlorid	Carbon Dioxid, Percentage by Volume	Remarks
Schmidt (Leipsic, 1850).....	15.3	....	.. ..	...	...	...	.....	....	Hydrocephalus, adult
	7.0	....	.. ..	...	...	...	.....	....	Hydrocephalus, fetus
Yvon (J. de pharm. et de chim. **4**: 240, 1877)	8.0	....	.....	...	...	...	.....	....	Fetus
Mestrezat (J. de pharm. et de chim. **29**: 572, 1909)	6.2	....	.....	...	...	...	.....	....	Hydrocephalus, necropsy
	7.1	....	.....	...	...	...	.....	....	Mixture of 20 normal fluids
	6.8	20.7	322.4	3.0	...	...	600-750	....	
Myers (J. Biol. Chem. **6**: 115, 1909).....	....	14.9-28.2	.....	...	...	...	.....	....	Fifteen insane patients
Halverson and Bergheim (J. Biol. Chem. **29**: 337, 1917)	5.1	....	.....	...	...	...	.....	....	Normal and diseases of nervous system
McVicar and Ross (J. Lab. & Clin. Med. **9**: 87, 1923)	....	10.5	365	...	...	...	.....	....	Various diseases
Barrio (J. Lab. & Clin. Med. **9**: 54, 1923)..	4.6-6.1	....	.....	1.4-6.1	1.5-2.7	...	.....	....	Syphilis
Weston and Howard (Arch. Neurol. & Psychiat. **8**: 179, 1922)	5.3	12.7	331	2.4	...	...	.. .	....	Manic-depressive insanity
Haurowitz (Ztschr. f. physiol. Chem. **128**: 290, 1923)	5.4	13.0	332	2.5	...	442	.....	....	
Pineus and Kramer (J. Biol. Chem. **57**: 463, 1923)	4.8	15.1	352	...	1.23	...	732	59	Normal
	4.95	14.9	342.2	...	1.38	...	716	54.1	Pathologic
Cohen (Quart. J. Med. **17**: 289, 1924).....	....	....	.....	...	1.64	...	.....	....	Normal
Nowicka (Arch. de méd. d. enf. **27**: 726, 1924)	....	....	.....	...	...	...	733	....	Normal
							510-680	....	Tuberculous meningitis
Behrendt (Monatschr. f. Kinderh. **27**: 458, 1924)	5.0	....	.....	...	...	...	.....	....	Normal infants and spasmophilia
Critchley and O'Flynn (Brain **47**: 337, 1924)	6.2	....	.....	...	...	...	.....	....	Various diseases
Shih-Hao (China M. J. [Oct.] 1924).....	3.3, 3.8	....	.....	...	1.41, 1.44	...	.....	....	Two cases tetany
	5.9, 5.9	....	.....	...	1.35, 3.80	...	.....	....	Same after treatment
Leicher (Deutsche. Arch. f. klin. med. **141**: 196, 1922)	5.0	....	.....	...	...	...	.....	....	Normal and pathologic

* Expressed in milligrams per hundred cubic centimeters of fluid.

they found 4.0 mg. and 5.3 mg. per hundred cubic centimeters, and in one case of chronic tetany 4.0 mg. (approximately). It is difficult to evaluate their work however, because of the unusual results they report in some of their examinations. This is particularly true in their determinations of the blood calcium, from which they report results as high as 19 mg. per hundred cubic centimeters. Behrendt [13] determined the ionized and total calcium in the cerebrospinal fluid of normal infants and in those with spasmophilia. He found an average total content of 5.0 mg. per hundred cubic centimeters for both healthy infants and those with spasmophilia, including exceptionally severe cases of this condition. The average value of the ionized calcium was 20 per cent. of the total (or 1.0 mg. per hundred cubic centimeters), and this value was not influenced by the presence of spasmophilia. Shih-Hao [14] reports the calcium content of the cerebrospinal fluid reduced in two cases of active tetany occurring in Chinese girls, aged 15 and 16 years. The content returned to normal after treatment with cod liver oil (Table 1).

Our own determinations of the inorganic constituents of the blood and cerebrospinal fluid in seventeen cases of spasmophilia are given in Table 2. The total amount of blood and cerebrospinal fluid required was withdrawn at one time whenever possible. Twenty cubic centimeters of spinal fluid was necessary for the different procedures. We used the following methods: for calcium and potassium, the methods of Kramer and Tisdall; [15] for sodium, the method of Kramer and Tisdall [16] for most of the determinations; after Feb. 14, 1925, the method described by Kramer and Gittleman; [17] for chlorids (whole blood), Whitehorn's [18] method; for inorganic phosphorus, a slight modification of the Bell-Doisy [19] method, which consisted in centrifugalization instead of filtration after the precipitation of proteins; for carbon dioxid, the Van Slyke-Cullen [20] method.

A summary giving the averages of the first and last estimations in the individual cases is presented in Tables 3 and 4. The first determinations were made soon after admission, when the calcium content of the blood was markedly reduced and when the patients showed symptoms of spasmophilia. The last determinations were made after the patients were cured of rickets and spasmophilia.

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13. Behrendt: Monatschr. f. Kinderh. **27**:458 (Jan.) 1924.
14. Shih-Hao: China M. J. (Oct.) 1924.
15. Tisdall, F. F.: J. Biol. Chem. **56**:439 (June) 1923; Kramer, B., and Tisdall, F. F.: J. Biol. Chem. **46**:339 (April) 1921.
16. Kramer, B., and Tisdall, F. F.: J. Biol. Chem. **46**:467 (May) 1921.
17. Kramer and Gittleman: J. Biol. Chem. **62**:353 (Dec.) 1924.
18. Whitehorn: J. Biol. Chem. **45**:449 (Feb.) 1921.
19. Bell, R. D., and Doisy, E. A.: J. Biol. Chem. **44**:55 (Oct.) 1920.
20. Van Slyke, D. D., and Cullen, G. E.: J. Biol. Chem. **30**:289 (June) 1917.

TABLE 2.—*Inorganic Constituents of Blood and Cerebrospinal Fluid in Cases of Spasmophilia* *

Case	Date	Calcium		Potassium		Sodium		Inorganic Phosphorus		Sodium Chlorid		Chlorin		Carbon Dioxid (% by Vol.)		Remarks
		Blood	Fluid	Blood	Fluid	Blood	Fluid	Blood	Fluid	Blood	Fluid	Blood	Fluid	Blood	Fluid	
1. G. M.	1/ 2/24	5.4	4 8	....	....	.. ..	.....	3.2	1.9	503.1	669.7	304.0	405.8	....	....	Adm. 12/31/23. Age, 8 mos. Diagnosis: rickets; spasmophilia; pyelitis. Ch. pos. KOC 1.75
	4/ 7/24	9 9	5.2	....	....	.....	.....	4.1	1.3	521.8	717.0	316.2	434.5	....	....	After treatment
2. G. C.	1/ 9/24	7.4	4.7	21.7	11.2	.....	.....	4.8	1.4	498.8	714.8	302.3	433.2	....	....	Adm. 12/22/23. Age, 5 mos. Diagnosis: cerebral birth injury; rickets; spasmophilia. Ch. pos. Frequent convulsions since birth. KOC > 6. 1/11/24, KOC 3.0
3. W. S.	4/28/24	6.8	4.9	21.5	11.9	318.6	320.3	4.6	1.7	465.1	708.3	281.9	429.3	51.3	46.6	Adm. 4/26/24. Age, 9 mos. Diagnosis: rickets; spasmophilia. Ch. pos. KOC 1.25
4. B. D.	4/14/24	6.1	3.8	17.4	9.7	291.9	287.9	5.8	1.9	508.7	734.7	308.3	445.2	46.3	43.5	Adm. 4/13/24. Age, 10 mos. Diagnosis: rickets; spasmophilia; pyelitis. Convulsions: 2 mos., 1 mo., and several during the week previous to adm. Laryngospasm. Ch. pos. KOC 2.0
5 R. G	4/14/24	6.4	4.8	17.5	9.2	297.3	287.0	5.4	1.95	508.8	695.6	308.3	421.5	....	....	Adm. 4/11/24. Age, 10 mos. Diagnosis: rickets; spasmophilia. Ch. pos. Laryngospasm. Convulsions: 3 mos., 1 mo., 2 wks., and 2 days previous to adm. KOC 3.0. Died during convulsion
6. M. J.	4/30/24	6.9	4.6	20.1	12.3	308.6	312.2	4.0	1.5	451.6	694.8	273.7	421.1	48.3	42.2	Adm. 4/29/24. Age, 2 yrs. 4 mos. Diagnosis: spasmophilia; nasopharyngitis. Ch. pos. Tr. pos. KOC 3.0. Roentgen ray of wrist: no evidence of rickets
	5/ 5/24	9.7	4.2	19.1	9.2	.....	.....	5.2	1.9	440.8	694.8	267.2	421.1	48.1	44.5	KOC > 5.0
	6/ 2/24	10.4	5.0	21.9	11.25	296.8	305.9	5.4	1.55	504.0	721.7	304.9	437.4	41.0	41.0	After treatment
7. M. M.	12/ 4/24	8.5	5.0	24.4	11.1	309.5	326.7	3.3	1.3	508.2	683.3	308.0	414.1	....	....	Adm. 11/18/24. Age, 14 mos. Diagnosis: rickets; spasmophilia; otitis media. Ch. pos. Tr. pos. KOC 2.2
8. C. H.	1/16/25	6.2	3.7	21.4	11.4	305.5	307.0	5.9	1.8	509.2	724.2	308.6	438.9	34.9	35.9	Adm. 1/16/25. Age, 8 mos. Diagnosis: rickets; spasmophilia. Ch. pos. Tr. pos. Convulsions: 3 wks., 5 days before adm., and two on day of adm. KOC 1.0
	1/23/25	6.7	4.9	....	....	.....	.....	4.6	1.8							
	1/28/25	8.7	4.6	....	....	.....	.....	5.5	1.7							
	2/19/25	10.1	5.0	23.5	10.9	.....	.....	5.6	2.0	436.0	719.4	295.4	487.4	. ..	....	After treatment
9. K. T.	1/26/25	4.9	4.1	22.5	13.0	318.5	316.8	7.6	1.8	508.0	754.5	307.9	457.3	....	....	Adm. 1/26/25. Age, 12 mos. Diagnosis: rickets; spasmophilia. Ch. pos. KOC 1.0. Convulsions: 5 days before adm., and on day of adm. Spontaneous tetany several days before adm.
	1/27/25	5.1	4.4	....	....	.....	.....	6.5	1.7							
	2/26/25	9.7	4.5	23.8	11.55	315.0	327.3	4.5	1.5	510.5	734.8	309.4	439.3	....	....	After treatment

10. T. T.	1/ 2/25	5.7	5.4	20.9	11.65	316.6	321.2	3.9	1.75	489.2	724.2	296.5	438.9	....	....	Adm. 12/26/24. Age, 15 mos. Diagnosis: rickets; spasmophilia; bronchopneumonia. Convulsion 3 days before adm. Ch. pos. Laryngospasm. KOC 2.0
	2/14/25	9.6	4.6	17.2	11.6	332.4	340.8	5.4	1.5	449.6	741.8	317.7	524.2	....	....	After treatment
11. J. L.	1/26/25	7.2	4.5	22.7	15.0	310.4	321.3	4.3	1.5	508.0	715.3	307.9	433.5	....	....	Adm. 1/9/25. Age, 11 mos. Diagnosis: rickets; spasmophilia; bronchopneumonia; otitis media. Ch. neg. 1/12/25: blood Ca 7.9 mg., inorg. P, 2.3 mg., KOC 4.75. 1/20/25: Ch. pos.
	2/26/25	9.9	4.8	21.1	11.6	334.1	320.5	4.2	1.45	557.8	705.0	338.1	427.3	....	....	After treatment
12. J. J.	11/14/25	6.5	5.4	16.8	11.3	327.3	296.4	5.2	1.7	468.4	755.4	283.7	457.8	33.7	34.7	Adm. 11/23/24. Age, 6 mos. Diagnosis: rickets; spasmophilia; encephalitis (150 mononuclears in spinal fluid, increased globulin). Three convulsions on day adm. Ch. pos. KOC 1.2
	11/29/24	7.8	5.9	27.2	12.4	311.8	311.3	4.0	1.5	485.1	703.9	294.0	426.6			
	1/ 5/25	10.2	4.7	22.4	12.5	309.5	329.8	4.3	1.7	526.7	709.2	319.2	429.8	....	....	After treatment
13. R. K.	2/14/25	6.2	4.3	23.3	8.4	309.9	323.1	4.6	1.4	475.5	722.5	288.2	437.9	....	....	Adm. 2/12/25. Age, 14 mos. Diagnosis: rickets; spasmophilia; nasopharyngitis, acute. Convulsions: 8 mos., 5 days, 4 days, 2 days and 1 day before adm.; two on day of adm. Ch. pos. KOC 3.5
	3/ 5/25	8.9	4.3	19.2	11.0	318.4	320.6	6.8	1.6	446.8	705.8	270.8	427.8	....	....	After treatment
14. J. F.	3/12/25	6.0	4.0	....	....	.....	.....	3.3	2.0	.....	.....	.....	.....	....	....	Adm. 3/5/25. Age, 11 mos. Diagnosis: rickets; spasmophilia; bronchopneumonia. Convulsions: 1 wk. before adm. and two on day of adm. KOC 9.0. Ch. neg. 3/9/25: KOC 5.0. 3/11/25: Ch. pos.
15. M. G.	3/12/25	6.0	5.1	24.9	12.8	322.4	325.3	4.4	1.7	480.9	696.4	290.3	422.1	43.9	46.7	Adm. 3/11/25. Age, 17 mos. Diagnosis: rickets; spasmophilia; nasopharyngitis, acute. Convulsions: 12 mos., 3 mos. and 3 days before adm. Ch. pos. KOC 3.0. 3/13/25: KOC 1.0
	3/25/25	10.5	5.2	25.9	12.8	328.7	333.2	6.0	1.6	485.4	735.3	294.2	445.7	43.4	45.4	After treatment
16 G. C.	3/ 9/25	8.0	4.5	25.1	11.8	300.5	319.7	2.8	1.2	523.1	705.9	317.0	427.8	....	....	Readm. 3/7/25 (see Case 2 above). Age, 20 mos. Convulsions less frequent since last adm. Ch. pos. KOC 2.5
17. G. T.	3/18/25	8.3	4.5	19.9	11.9	326.9	321.9	5.0	1.8	501.1	715.4	303.7	433.6	....	....	Adm. 3/17/25. Age, 2¼ yrs. Diagnosis: rickets; spasmophilia. Ch. pos. KOC 1.2. Convulsions: first when 15 mos. old; five during the following year and five in one day, one week before adm.
	3/25/25	9.8	5.3	21.3	12.0	338.3	337.2	6.0	1.6	450.6	702.7	273.1	425.9	....	....	After treatment

* Expressed in milligrams per hundred cubic centimeters. Ch. = Chvostek's sign. Tr. = Trousseau's sign.

TABLE 3.—*Average Concentration of Inorganic Constituents in Blood and Cerebrospinal Fluid in Cases of Spasmophilia* *

	Calcium	Potassium	Sodium	Inorganic Phosphorus	Sodium Chlorid	Chlorin	Carbon Dioxid Percentage by Volume
Blood	6.6	21.3	311.7	4.6	494.2	299.4	43.1
Spinal fluid	4.6	11.5	313.3	1.7	713.4	432.4	41.6

* Expressed in milligrams per hundred cubic centimeters.

TABLE 4.—*Average Concentration of Inorganic Constituents of Blood and Cerebrospinal Fluid in Cases of Spasmophilia Following Cure* *

	Calcium	Potassium	Sodium	Inorganic Phosphorus	Sodium Chlorid	Chlorin	Carbon Dioxid Percentage by Volume
Blood	9.9	21.6	321.6	5.2	488.9	303.9	42.1
Spinal fluid	4.86	11.7	326.9	1.6	719.3	447.9	43.2

* Expressed in milligrams per hundred cubic centimeters.

The only significant difference between the two groups is the usual decrease in the calcium content of the blood serum during the active phase. The average calcium content of the cerebrospinal fluid is practically the same in the two groups. In only two cases (Cases 4 and 8) do we find the calcium content of the cerebrospinal fluid noticeably lower than in the other cases. If we consider in one group the patients having one or more convulsions on the day of the first blood and spinal fluid examination, we do notice a slightly lower average calcium content in both the blood serum and the spinal fluid. This difference is shown in Table 5 and may be considered significant from a statistical point of view, but the small size of the series does not permit any conclusions to be drawn. The low calcium content of the dried brain in experimental and infantile tetany reported by the majority of the observers noted in the foregoing, we believe to be due to the general calcium deficiency of the body tissues and to the fact that it is not dependent on the calcium level in the cerebrospinal fluid.

TABLE 5.—*Concentration of Calcium in Blood and Cerebrospinal Fluid in Cases of Spasmophilia with Convulsions* *

Case	Blood Calcium	Spinal Fluid Calcium
4	6.1	3.8
8	6.2	3.7
9	4.9	4.1
13	6.2	4.3
14	6.0	4.0
Average	5.9	4.0
Average for entire series	6.6	4.6

* Expressed in milligrams per hundred cubic centimeters.

TABLE 6.—*Inorganic Constituents of Blood and Cerebrospinal Fluid in Various Diseases* *

Case	Date	Calcium		Potassium		Sodium		Inorganic Phosphorus		Sodium Chlorid		Chlorin		Carbon Dioxid (% by Vol.)		Remarks
		Blood	Fluid	Blood	Fluid	Blood	Fluid	Blood	Fluid	Blood	Fluid	Blood	Fluid	Blood	Fluid	
1. H. G.	1/ 6/24	11.3	5.2	23.8	12.2	.....	.....	4.5	1.5	460.1	717.0	278.8	434.5	....	....	Age, 3 yrs. Polioencephalitis
2. B. K.	2/ 5/24	11.1	5.2	....	....	.....	.....	3.4	1.6	465.7	710.0	281.9	430.3	....	....	Age, 10 yrs. Chorea
3. R. M.	3/24/24	11.4	5.0	24.8	10.0	.....	.....	4.4	1.4	470.8	721.7	285.3	437.4	....	....	Age, 5 yrs. Chorea
4. I. M.	2/21/24	9.5	6.6	....	....	.....	.....	2.8	1.3	.....	.....	.....	.....	....	....	Age, 14 mos. Rickets; otitis media
5. G. K.	1/21/24	8.9	5.1	26.3	13.8	.....	.....	6.8	1.6	545.3	722.1	330.4	437.6	....	....	Age, 21 mos. Cerebral birth
	1/24/24	9.3	4.6	....	....	.....	.....	6.1	1.45	504.8	677.3	304.0	410.4	....	....	Palsy; convulsions since 8 months old
6. J. B.	5/23/24	9.1	6.8	19.9	14.5	311.3	306.4	2.4	1.9	475.8	660.3	288.4	400.2	60.7	43.3	Age, 12 mos. Bronchopneumonia, (B. influenzae) an influenzal meningitis
7. B. L.	6/ 4/24	9.6	5.7	....	....	.....	.....	4.3	1.7	431.3	693.8	261.4	423.5	....	....	Age, 13 yrs. Psychoneurosis
8. G. M.	11/10/24	12.6	4.2	24.5	9.4	299.1	.....	8.6	1.65	371.7	703.9	225.3	426.6	....	....	Age, 6 mos. Normal child
9. F. M.	5/16/24	10.5	5.2	21.1	12.35	314.5	313.1	4.5	1.4	474.5	728.9	287.6	441.8	....	....	Age, 7 yrs. Polioencephalitis
10. J. B.	10/13/24	10.2	4.9	21.4	10.1	297.8	302.8	2.5	1.45	458.7	681.6	278.0	413.1	....	....	Age, 6 mos. Miliary tuberculosis; tuberculous meningitis; rickets
11. F. J.	11/24/24	11.7	6.6	21.0	11.95	313.8	311.3	5.2	2.1	499.3	701.3	302.6	425.0	....	....	Age, 6 mos. Cerebral birth; palsy; atelectasis, right upper lobe; frequent convulsions for 4 weeks before admission
12. A. E.	2/20/25	9.3	6.9	14.9	16.1	336.4	338.6	4.0	3.1	600.9	786.5	364.2	476.7	....	....	Age, 14 mos. Influenzal meningitis; suppurative arthritis, left knee

* Expressed in milligrams per hundred cubic centimeters.

The estimations of carbon dioxid show marked individual variations and are altogether unsatisfactory. This we believe was due to the excessive crying of some of the patients and presented a variable factor which could not be controlled.

For comparison with the cases of spasmophilia, we determined the same inorganic constituents of the blood and cerebrospinal fluid in a second series of cases with various diseases. The results are given in Table 6.

No significant changes were found. In the two cases of influenzal meningitis, the spinal fluid calcium was higher than normal and in one of these cases (Case 12), the inorganic phosphorus was unusually high and the potassium content of the spinal fluid was greater than that of the blood. Loeb, Atchley and Palmer [21] have shown that in transudates and exudates, the calcium content approaches that of the blood serum, while the potassium content is lower than that of the blood serum. They did not estimate the inorganic phosphorus. So, in cases of purulent meningitis with a much higher protein content than normal in the spinal fluid, it is reasonable to conclude that the calcium content will be proportionately increased. In two other cases (Cases 4 and 11, Table 6), however, with otherwise normal spinal fluids, the calcium content was greater than normal, which negatives any conclusions concerning the two cases of purulent meningitis. A larger number of purulent meningitis cases may show some definite change in the inorganic constituents of the spinal fluid.

SUMMARY AND CONCLUSIONS

1. The inorganic constituents of the blood and cerebrospinal fluid were determined in seventeen cases of spasmophilia.

2. No significant changes from normal were found, except the usual decrease in the calcium content of the blood during the active phase.

3. In the cases of spasmophilia with convulsions on the day of the first examination, the calcium content of the blood serum and spinal fluid was found somewhat lower than the average for the entire series. No conclusions are warranted, however, from such a small series.

4. Similar determinations were made in twelve cases with various diseases. No significant changes from normal were found in this group.

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21. Loeb, R. F.: Atchley, D. W., and Palmer, W. W.: J. General Physiol. **4**:591 (May) 1922.

THE VAN DEN BERGH TEST FOR ICTERUS IN THE BLOOD OF INFANTS*

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In 1913, van den Bergh and Snapper [1] described a test for bilirubin in the blood, which was really an application of the diazo reaction. Not much was done with respect to this test, probably because of the war.

In 1918, van den Bergh [2] published a monograph giving the test in detail and also a modification of it. In this treatise he states his belief that there are different types of bilirubin and that these can be distinguished by this reaction. These two reactions are mentioned by him as the direct and the indirect reactions. He believes the direct reaction is due to the type of bile which is present as the result of mechanical obstruction. The indirect reaction is found in cases in which no such mechanical obstruction exists.

He states that the difference between the types of bilirubin is based not alone on the difference in their reactions to the test, but that they have other distinctive features. In the type which shows the direct reaction, if the blood serum is precipitated with alcohol, the precipitate shows a marked adsorption of the biliary coloring matter, while in those cases which show the indirect reaction, no such adsorption is manifested. The bilirubin which gives the direct reaction is more easily oxidized into biliverdin than that which gives the indirect reaction.

It is interesting to note that van den Bergh found that a direct reaction was obtained in all cases in which there was a mechanical obstructive jaundice, whether this was light or severe.

The problem which primarily concerned us was to determine: first, whether the findings of van den Bergh would hold true in infants; second, and especially, the nature of the test in cases of icterus neonatorum.

THE DIRECT REACTION

Most of the work previously done with this test has been on adults. Andrewes [3] made the test in 184 cases and agreed in general with the

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1. Van den Bergh and Snapper: Deutsch. Arch. f. klin. Med. **110**:540, 1913.
2. Van den Bergh, A. A. H.: Der Gallenfarbstoff im Blut, Leiden, 1918.
3. Andrewes, C. H.: Quart. J. Med. **19**:69, 1924.

findings of van den Bergh, though he says that at the onset, in obstructive cases, only an indirect or diphasic reaction may occur. McNee [4] reports only four cases which, in general, correspond to the findings of van den Bergh. Jones [5] in his five cases of obstructive jaundice always got the direct reaction. Lepehne's [6] work agreed with van den Bergh's findings in the adult also.

THE INDIRECT REACTION

We see, therefore, that so far as the published reports are concerned, the agreement with van den Bergh's original contention is well established so far as it relates to the adult. In children, investigations have been confined mostly to cases of icterus neonatorum. In Lepehne's large series, seven cases of icterus neonatorum showed the indirect reaction. In this series, the blood was taken from the heel. Cserna and Liebman [7] found that from the umbilical blood of thirty-four new-born infants, the indirect reaction only was obtained. Zamorani [8] had similar results in four cases of icterus neonatorum. Knoepfelmacher and Kohn [9] obtained the indirect reaction in fifty specimens of umbilical blood from the new-born and also from the blood and the meconium of five children with icterus neonatorum. It is interesting to note that in the bile from the gallbladder of three stillborn infants examined by them, direct reactions were obtained each time.

Another finding of great interest is that of Hoffmann,[10] who obtained the direct reaction in a case of icterus neonatorum gravis, which he believed was due to obstructive jaundice caused by inflammation and enlargement of the lymph tissue about the bile ducts. Schiff and Faerber [11] obtained an indirect reaction in twenty-six out of twenty-seven cases of icterus neonatorum. The twenty-seventh case showed a direct reaction but was of the type of familial icterus gravis. We see, therefore, that there is general agreement that icterus neonatorum simplex gives only the indirect reaction, while icterus gravis in one and familial icterus gravis in another each gave the direct reaction.

ORIGIN OF BILIRUBIN

If the van den Bergh reaction is to be considered, as has been claimed by some, to distinguish the origin of bilirubin, then its importance is of the greatest value.

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4. McNee, J. W.: Brit. M. J. **1**:716 (May 6) 1922.
5. Jones: M. Clin. N. Am. **6**:1089, 1923.
6. Lepehne, G.: Deutsch. Arch. f. klin. Med. **135**:79 (Jan.) 1921.
7. Cserna and Liebman: Klin. Wchnschr. **2**:2122, 1923.
8. Zamorani: Riv. di clin. pediat. **23**:1, 1925.
9. Knoepfelmacher, W., and Kohn: Monatschr. f. Kinderh. **22**:1, 1921.
10. Hoffmann, W.: Jahrb. f. Kinderh. **105**:155, 1924.
11. Schiff, E., and Faerber, E.: Jahrb. f. Kinderh. **97**:245 (March) 1922.

Most of the investigators are inclined to believe that the direct reaction indicated a hepatogenous origin of the bilirubin, while the indirect indicated an anhepatogenous origin. The importance of this for our subject does not need emphasis when one remembers the long-standing controversy regarding the nature of icterus neonatorum.

METHOD

The technic used by us was that given by van den Bergh [12] in an article appearing in 1921, and is as follows:

Three or 4 c.c. of blood are obtained, as for the Wassermann test. Care must be taken to prevent even the slightest hemolysis or the results will be inaccurate.

The blood is centrifuged and the clear serum pipetted off. The serum is divided into two portions. To one is added an equal volume of 95 per cent. alcohol; this mixture is centrifuged and the serum pipetted off. To the clear fluids, one of which is undiluted serum, the other an alcoholic dilution with the precipitated protein removed, equal volumes of a mixture of the following are added:

Solution 1.—Sulphanilic acid, 1 part; concentrated hydrochloric acid, 15 parts; sufficient water to make 1,000 parts.

Solution 2.—Aqueous solution of sodium nitrite, 0.5 per cent.

The reagent for the test consists of Solution 1, 25 c.c.; Solution 2, 0.75 c.c. The mixture of the two solutions must be absolutely fresh—never more than one day old.

When equal parts of the reagent are added to the serum and to the alcoholic solution, a positive test is indicated by the formation of a reddish-violet color, which may appear at once or after some time. To the undiluted serum, a violet color appearing within fifteen seconds constitutes a direct reaction. A reaction occurring within from fifteen seconds to an hour is considered indirect. The alcoholic dilution gives only the "indirect" reaction, usually at once.

We have divided the cases observed into five groups:

1. Icterus neonatorum.
2. Icterus complicating acute respiratory infections.
3. Icterus resulting from destruction of liver cells following administration of neo-arsphenamin.
4. Acute catarrhal jaundice.
5. Obstructive jaundice.

GROUPS

Group 1.—In all, twelve cases were tested, five being cases in which umbilical cord blood was used. The reaction was indirect in each. Three of the babies

12. Van den Bergh, A. A. H.: Presse méd. **29**:441 (June 4) 1921.

developed jaundice, the other two were free. Of the seven cases of icterus neonatorum in which blood obtained from the sinus was used, all gave indirect reactions.

GROUP 2.—Three cases of jaundice complicating acute respiratory infection were noted.

Case 1.—O. W., a premature infant, one of twins, entered the hospital with icterus neonatorum, at which time an indirect van den Bergh reaction was obtained. Two months later, she again developed jaundice with signs of an upper respiratory infection. The van den Bergh reaction was indirect on this occasion. The jaundice cleared up after about a week.

Case 2.—J. Z., a premature infant, became jaundiced when 6 weeks old. The jaundice appeared at the same time as that of the first baby (Case 1). The jaundice was mild, lasted for a few days only and gave no signs of being of an obstructive nature. The van den Bergh reaction was indirect.

Case 3.—E. S., a premature infant, had acute gastro-intestinal disturbance with upper respiratory infection. This child became slightly jaundiced for a few days. There was no sign of obstruction. The van den Bergh reaction was indirect.

GROUP 3.—One case of jaundice following the administration of arsphenamin.

D., aged 4 weeks, was admitted to the hospital Nov. 7, 1924, with a history of bleeding from the umbilicus, the mouth and the anus for twenty-four hours. The bleeding time was one hour and forty minutes, coagulation time, seventeen minutes. The Wassermann test was 4 plus, and the administration of neo-arsphenamin was begun at once. Doses of 50 mg. of neo-arsphenamin were given intraperitoneally, three days apart, and two weeks later (Nov. 22), the child became deeply jaundiced. The van den Bergh reaction was indirect. The treatment was continued and the jaundice persisted. The van den Bergh test was repeated twice at intervals of two weeks; all three reactions were indirect. The child was still jaundiced when death occurred, two months after admission. Necropsy showed no obstruction of the bile passage.

GROUP 4: *Case 1.*—L. T., an infant, aged 1 month, entered the hospital with a vague history of jaundice since birth. The jaundice was marked; there were no signs of obstruction. The child was dehydrated and appeared acutely ill. The jaundice deepened after admission, the general condition grew worse, and the child died seventeen days after admission. The van den Bergh test was indirect on two occasions at intervals of ten days. The spinal fluid was clear. The Wassermann test was negative. Necropsy showed an acute catarrhal condition of the gallbladder.

Case 2.—A girl, aged 4 years, entered the hospital with moderate jaundice of five days' duration, and a history of clay-colored stools. She had no other symptoms, and there were no signs of obstruction. No acholic stools were noticed after entering the hospital. The liver was enlarged 4 cm. below the costal margin; the spleen was palpable. The Wassermann test was negative. The van den Bergh reaction was indirect. The jaundice cleared up gradually and the patient returned home after nineteen days. The diagnosis was acute catarrhal jaundice (convalescent).

GROUP 5.—A boy, aged 11 months, whose history previous to adoption, as obtained from the physician, was that the child had been jaundiced since birth. He was adopted when 4½ months old. The jaundice had persisted up to the time of admittance to the hospital. The child weighed only 9 pounds (4 kg.) on entering, and, according to his foster mother's statement, he had never gained at all. No diarrhea nor vomiting was present but the stools were copious, hard and white, and occasionally green (probably due to spinach). The child had not had any acute infections; he was intensely jaundiced; the liver was 3 cm. below the costal margin, the spleen was moderately enlarged and firm, and all the lymph glands were enlarged. The heart was enlarged

and there was a question as to the presence of a murmur. The Wassermann test was negative, and the fragility test normal. The van den Bergh test was made five times; two gave direct and three indirect reactions. During this time, there was some remission of the jaundice, but always with acholic stools. Repeated tests for bile in the stool were negative. The child was discharged unimproved with the diagnosis of suspected congenital defect of bile passages.

SUMMARY

These results agree quite well with those of other investigators who have studied the van den Bergh reaction in simple icterus neonatorum. Both from the umbilical blood and from the blood serum of the infant after the jaundice had developed only the indirect reaction was obtained.

In the three cases of jaundice in the course of acute respiratory infections, and in the one case following administration of neo-arsphenamin, the reactions were all indirect, which findings agree with the contention of van den Bergh.

In the two cases of catarrhal jaundice only indirect reactions were seen; in the one case of obstructive jaundice the results were so irregular as to be of questionable value.

The evidence here presented is such as to raise a doubt as to the value of the van den Bergh reaction as a method of differentiating between obstructive and nonobstructive types of jaundice in infants and in young children.

ACRODYNIA *

A CLINICAL STUDY OF SEVENTEEN CASES

F. C. RODDA, M.D.

MINNEAPOLIS

REVIEW OF THE LITERATURE

A certain train of symptoms affecting infants and young children has recently been designated as "acrodynia." In 1919, Bilderback [1] reported ten cases of this condition in children presenting peculiar nutritional, neurologic and dermatologic disturbances. These case reports were sent to Dr. John Morse who, recognizing findings suggestive of pellagra, in turn referred them to Dr. Weston of Columbia. After careful study, Weston [2] decided that the condition was not pellagra and applied the name acrodynia to the disease. In 1920, Byfield [3] reported a series of seventeen cases presenting similar symptoms. Being impressed with the neurologic findings, he entitled his report "A Polyneuritic Syndrome Resembling Pellagra-Acrodynia?' His report was so complete that but little has been added by numerous later reports. In 1921, Brown [4] reported eight typical cases. After careful clinical and metabolic studies, he concluded that acrodynia was not a deficiency disease, but rather the expression of some toxic condition following upper respiratory infections. Since 1921, numerous cases have been reported from various sections of the United States by Field,[5] Davis,[6] Vipond,[7] Cartin,[8] Giffen,[9] McNeal,[10] Emerson,[11]

* Received for publication, May 9, 1925.

* Read before the American Pediatric Society, Washington, D. C., May, 1925.

1. Bilderback, J. B.: A Group of Cases of Unknown Etiology and Diagnosis, Northwest Med. **19**:263 (Oct.) 1920.
2. Weston, W.: Acrodynia, Arch. Pediat. **37**:513 (Sept.) 1920.
3. Byfield, A. H.: A Polyneuritic Syndrome Resembling Pellagra-Acrodynia (?) Seen in Very Young Children, Am. J. Dis. Child. **20**:347 (Nov.) 1920.
4. Brown, A.; Courtney, A. M., and MacLachlan, I. F.: A Clinical and Metabolic Study of Acrodynia, Arch. Pediat. **38**:609 (Oct.) 1921.
5. Field, M. C.: Erythredema, Report of a Typical Case, Arch. Pediat. **39**: 116 (Feb.) 1922.
6. Davis, C. M.: Acrodynia, Arch. Pediat. **39**:611 (Sept.) 1922.
7. Vipond, A. E.: Acrodynia and Its Probable Causation, Arch. Pediat. **39**:699 (Nov.) 1922.
8. Cartin, H. J.: Acrodynia, Pennsylvania M. J. **24**:287 (Feb.) 1921.
9. Giffen, S. D.: Acrodynia, J. Michigan State M. S. **23**:8 (Jan.) 1924.
10. McNeal, M. D.: Report of Five Cases of So-Called Acrodynia, Minnesota Med. **5**:153 (March) 1922.
11. Emerson, P. W.: A Case of Acrodynia, J. A. M. A. **77**:285 (July 23) 1921.

Zahorsky [12] and others. The striking similarity of the numerous reports convinces one that this must be a clinical entity.

From the early reports in this country, it appeared that this was a new disease. But Swift [13] of Adelaide, Australia, in 1914 reported fourteen cases of the same clinical picture under the name "erythredema." Wood [14] of Melbourne, in 1921, reported that he had observed such cases for thirty years and that his predecessor, Snowball, had long tabulated such cases as "raw-beef hands and feet." Because of the striking skin changes, Littlejohn [15] of Sidney had recognized the same group of symptoms under the term "pink disease." Thursfield [16] of London has chosen the name "dermato-polyneuritis" in an endeavor to fix at least a partial pathologic basis in the terminology of the disease. So what had at first appeared to be a new disease, produced by diet deficiency or as an aftermath of the influenza epidemic of 1918, was found to be a long recognized clinical entity classified under various names. Doubtless, we have had such a disease always. It is a conjecture that before the advent of the roentgen ray, Wassermann and tuberculin reactions, it was often confused with syphilis and tuberculosis, or with malnutrition of undetermined origin. There is much discussion and confusion as to its nomenclature. (It is apparent from a study of case reports, under such titles as "raw-beef hands and feet," "pink disease," "erythredema," "dermatopolyneuritis" and "acrodynia," that observers are describing one and the same thing.)

Acrodynia (literally painful extremity), although it nicely describes the most typical symptom of the disease, takes no count of the nutritional and the neurologic findings. Butler,[17] in connection with a careful clinical and biopsy report of a case, suggests that the century-old term—acrodynia—might better be left as descriptive of the French garrison epidemic of 1828 (which was probably arsenical poisoning from contaminated wine), and that erythredema, the terminology used by Swift, be substituted for it. However, acrodynia has gained wide usage and unless the etiology and pathology of the disease are promptly demonstrated, it will probably remain in the literature.

SYMPTOMATOLOGY

What is the clinical picture of acrodynia? It is to be found in striking similarity in about 100 cases reported from Australia and from a

12. Zahorsky, J.: Semeiology of Pink Disease, J. A. M. A. **79**:1975 (Dec. 9) 1922.
13. Swift, D. H.: Lancet **1**:611 (April 27) 1918.
14. Wood, A. J.: M. J. Australia **1**:145 (Feb. 19) 1921.
15. Littlejohn, E. S.: Pink Disease—Erythredema, M. J. Australia **1**:689 (June 23) 1923.
16. Thursfield, J. H., and Paterson, D. H.: Dermato-Polyneuritis, Brit. J. Child. Dis. **19**:27 (March) 1922.
17. Butler, J.: Erythredema, Arch. Dermat. & Syph. **11**:166 (Feb.) 1925.

somewhat greater number reported in this country. A normal, thriving, well behaved child, between the ages of 1 and 3 years, rather abruptly shows extreme hyperirritability; loses appetite, sleeps poorly, perspires excessively and cries and whines constantly. Nothing the mother can do affords comfort. Miliaria of varying distribution and intensity develops. After a definite period, usually from two to four weeks, the characteristic changes in the hands and feet suddenly develop. The fingers and toes become red, swollen and edematous, present a fine maculopapular eruption not sharply demarcated, and are cold, clammy and somewhat cyanosed. Desquamation follows. The child is apparently distressed, and rubs and wrings the hands and often bites them. Older children describe pricking, burning sensations and obtain relief from immersion in cold water. The more severe types are the more chronic cases and almost beggar description. In addition to the foregoing symptoms, the children become extremely emaciated; maceration of the skin and pyodermia may be generalized and there is great muscular weakness, even paresis. The patient lies curled up, with the head buried in the pillow to relieve photophobia. The hair falls out or is pulled out. Salivation, ulceration of the gums and loss of teeth may be present. Food is refused, sleep is disturbed, no comfort can be given, and the child presents a picture of abject misery.

ETIOLOGY

The etiology of acrodynia is not yet clear. Because of its surmised resemblance to pellagra and the announcement of the "new" disease at the time when the medical world was much concerned with vitamins, it is not strange that this was thought to be a deficiency disease. Whatever the cause may be, it surely is not due to a deficiency in diet. Again, the announcement of the "arrival" of the disease soon after the epidemic of influenza suggested a relationship to the pandemic. But the condition continues to be found in children born since 1918, and case reports from Australia antedating the pandemic by half a century deprive acrodynia of this relationship. There is much proof, clinically, that acrodynia is the result of a chronic intoxication from upper respiratory infections. Whether such a strange disease, occurring rather rarely in so prevalent a field of infections, is the result of a specific organism or the reaction of a peculiar type of child to the more common infecting organisms cannot yet be stated.

COMMENT

A relationship to the influenza epidemic apparently is not borne out. In this series, two cases occurred in 1919, two in 1920, one in 1921, one in 1922, six in 1923, four in 1924 and one early in 1925.

TABLE 1.—*Histories of Patients Presenting Symptoms*

Case	Date	Age	Sex *	Season of Onset	Preceding Infection	Time from Infection to Onset of Acrodynia	Duration of Symptoms of Acrodynia	Presenting Complaints	Diet
1 W. P.	1919	17 mos.	♂	July	Diarrhea	2 mos.	2 mos.	Anorexia; loss of weight	Good
2 W. B.	1919	4 yrs.	♂	March	Influenza	2 mos.	2 mos.	Itching; loss of weight	Good
3 I. F.	1920	18 mos.	♀	April	Influenza	3 mos.	3 mos.	Weakness; loss of weight; miliaria	Good
4 P. W.	1920	7 yrs.	♀	Aug.	Diarrhea	2 mos.	6 mos.	Loss of weight	Good
5 M. B.	1921	18 mos.	♀	Sept.	Tonsillitis	1 mo.	1 wk.?	Loss of teeth	Good
6 K. K.	1922	18 mos.	♀	July	?	?	3 mos.	Loss of weight	Good
7 E. I	1923	6 yrs.	♀	Jan.	Influenza	1 mo.	2 yrs.	Burning sensation of feet	Good
8 L. S.	1923	13 mos.	♂	Feb.	?	?	2 mos.	Sleeplessness	Good
9 J. C.	1923	3 yrs.	♂	May	?	?	2 mos.	Weakness	Good
10 F. S.	1923	11 mos.	♂	April	Pertussis	2 mos.	1 mo.	Ulceration of gums; hyperirritability	Good
11 L. H.	1923	2 yrs.	♂	June	?	?	2 mos.	Loss of weight; restlessness	Good
12 L. R.	1923	2 yrs.	♀	Oct.	?	?	6 wks.	Photophobia	Good
13 J. O.	1924	30 mos.	♂	March	Grip	2 mos.	2 wks.	Hyperirritability	Good
14 M. S.	1924	18 mos.	♂	March	Diarrhea	?	6 wks.	Hyperirritability	Good
15 J. L.	1924	30 mos.	♀	July	?	?	6 wks.	Hyperirritability	Good
16 G. P.	1924	2 yrs.	♂	July	Grip	2 mos.	1 mo.	Anorexia; weakness	Good
17 D. M.	1925	15 mos.	♂	Dec.	Tonsillitis	1 mo.	2 wks.	Hyperirritability; sleeplessness	Good

* In this column, ♀ indicates female, ♂ male.

It is apparently a disease of infancy and early childhood. In this group the youngest patient was aged 11 months, the oldest was 7 years. Eleven (or 65 per cent.) of the patients in this series were between the ages of 1 and 2 years; fourteen (or 85 per cent.) between 1 and 3 years.

There appeared to be no sex distinction.

As to seasonal incidence, three cases occurred in the winter months, six in the spring, six in the summer and two in the fall. The larger number were seen in the late spring and early summer, following the greatest incidence of grippal infections.

A history of a preceding infection was elicited in eleven (or 65 per cent.) of these cases. Diarrhea appeared three times, but this was presumably parenteral, following upper respiratory infections. It is believed that careful observations would reveal the preceding upper respiratory infection in all cases. It is easily understood that a mother, concerned with the more distressing symptoms of acrodynia, might easily forget the more trivial premonitory symptoms.

In 60 per cent. of these cases, there was a definite time from the infection to the onset of the hyperirritability, that is, an incubation period of from one to two months.

The duration of symptoms averaged from one to three months. In one case, it was six months and in another two years.

The presenting symptoms varied somewhat with the observer, but hyperirritability and sleeplessness were most often noted.

There was no evidence of food deficiency. True, anorexia occurred in fifteen of the seventeen cases, but this was a symptom of the disease and not a cause. In not a single case could a faulty diet be determined.

Table 2, dealing with symptoms, physical and laboratory findings, is self-explanatory. The symptoms are tabulated in the order of their frequency. The first four symptoms—hyperirritability, hyperhidrosis, rubbing of hands and feet, the erythema and peculiar changes in the skin of hands and feet—were found in all cases. These symptoms are pathognomonic. Desquamation and generalized miliaria were found almost as frequently. Sleeplessness, anorexia, loss of weight and weakness, results to be anticipated from the preceding symptoms, were present in nearly all the cases. The neurologic findings, paresthesia and diminished reflexes, occurred in over half the cases. Alopecia occurred in nine, photophobia in eight and loss of teeth in three cases. One patient lost eight teeth. Infected tonsils, persistent nasal discharge and cervical adenitis, found in all cases, is reasonable evidence of a possible focal infection. I have never seen the condition in a child whose tonsils and adenoids had been removed. One should also consider the accessory nasal sinuses as possible foci of infection, but none were found in this series. The laboratory findings were of negative value. Leukocyte counts were high, moderate, normal or low and without relationship to peculiarity or severity of symptoms. Eleven cases had negative Wassermann reactions, sixteen gave negative Pirquet reactions, and pyuria was present in one case. Complicating disorders were found in only three cases, and appeared to have no etiologic relationship.

TREATMENT

Just as there is a marked similarity of clinical pictures in the case reports, there is as striking an agreement in the pessimistic attitude as regards therapy. Weston suggested dietetic and palliative treatment. Byfield stated forced feeding, even by gavage, is the mainstay, but added "if recovery is slow or a fatal outcome is feared, an attempt to remove the assumed foci is justified." Vipond reported two patients cured by the use of a vaccine prepared from material aspirated from enlarged glands. However, practically all observers state that the duration of the disease is usually from three months to two years, and the treatment symptomatic. Bilderback,[18] in a report as late as February, 1925, deplores our "therapeutic pauperism." Such, however, has not been my experience. True, the early patients suffered from lack of proper treatment, but they also suffered from lack of even a diagnosis. They eventually recovered,

18. Bilderback, J. B.: Acrodynia, J. A. M. A. **84**:495 (Feb. 14) 1925.

TABLE 2.—*Symptoms and Physical and Laboratory Findings*

Case	Hyperirritability	Hyperhidrosis	Rubbing of Hands and Feet, Scratching	Erythema, Coldness, Cyanosis, and Swelling of Hands and Feet	Desquamation	Miliaria, Maceration of Skin	Sleeplessness	Anorexia	Per Cent. Loss of Weight	Weakness	Paresthesias and Anesthesias	Diminished Reflexes	Alopecia and Trichotillomania	Photophobia	Loss of Teeth, Ulceration of Gums	Injected Tonsils	Nasal Discharge	Cervical Adenitis	Leukocytes	Wassermann Reaction	Pfiquet	Urinalysis	Complicating Disorders
1	+	+	+	+	+	+	+	+	23	+	0	+	0	+	0	+	+	+	19,000	neg.	neg.	neg.	0
2	+	+	+	+	+	+	+	+	20	+	0	+	0	0	0	+	0	+	20,000	neg.	neg.	neg.	0
3	+	+	+	+	+	+	+	+	30	+	0	+	0	+	0	+	+	+	11,000	neg.	neg.	neg.	0
4	+	+	+	+	+	+	+	+	32	+	0	+	0	+	(a) +	+	+	+	13,000	neg.	neg.	neg.	Pyodermia Pyelitis
5	+	+	+	+	+	+	+	+	32	+	0	+	0	+	0	+	+	+	17,000	neg.	neg.	pus +++	0
6–7	+	+	+	+	+	+	+	+	12	+	+	+	+	+	0	+	?	+	11,000	0	neg.	neg.	Hysteria?
8	+	+	+	+	+	+	+	+	15	+	+	+	+	+	0	+	+	+	7,000	0	neg.	neg.	0
9	+	+	+	+	+	+	+	+	25	+	+	+	+	+	0	+	+	+	8,000	neg.	neg.	neg.	0
10	+	+	+	+	+	+	+	+	24	+	+	+	+	+	0	+	+	+	12,000	neg.	neg.	neg.	0
11	+	+	+	+	+	+	+	+	0	+	+	+	+	+	0	+	+	+	12,000	neg.	neg.	neg.	0
12	+	+	+	+	+	+	+	+	10	+	+	+	+	+	0	+	+	+	11,000	?	?	neg.	0
13	+	+	+	+	+	+	+	+	10	+	+	+	+	+	0	+	+	+	?	?	?	neg.	0
14	+	+	+	+	+	+	+	+	20	+	+	+	+	+	0	+	+	+	10,000	neg.	neg.	neg.	0
15	+	+	+	+	+	+	+	+	0	+	+	+	+	+	0	+	+	+	13,000	neg.	neg.	neg.	0
16	+	+	+	+	+	+	+	+	12	+	+	+	+	+	0	+	+	+	?	neg.	neg.	neg.	0
17	+	+	+	+	+	+	+	+	20	+	+	+	+	+	0	+	+	+	9,800	neg.	neg.	neg.	0
																			7,000	?	neg.	neg.	

but convalescence was prolonged many months. In a few of the early patients, eventually the tonsils and adenoids were removed, not anticipating any effect on the disease, but simply to relieve the child of the handicap of a persisting upper respiratory infection. To our surprise the patients promptly recovered. There was speedy relief from perspiration, a return of appetite and sleep, a gain in weight, and lastly the disappearance of the peculiar skin findings. Since making these observations, the tonsils and adenoids have been removed as soon as a diagnosis was made.

TABLE 3.—*Treatment and Results*

Case	Forced Feeding, Including Yeast, Orange Juice, Cod Liver Oil	Treatment of Nose and Throat	Removal of Tonsils and Adenoids	Rate of Recovery	Degree of Recovery	Time Required for Recovery	Remarks
1	+	+	No	No improvement			Left hospital after 23 days; no diagnosis
2	+	0	No	Slow	Complete	5 months	Recovery during summer; diagnosis, polyneuritis
3	+	+	Adenoids	Slow	Complete	8 months	
4	+	0	Yes	Speedy	Complete	2 to 3 mos.	Speedy recovery after removal of tonsils and adenoids
5	+	+	No	Slow	Complete	1 year	
6	+	0	No	Slow	Complete	7 months	
7	+	0	No	No improvement			No improvement after one year
8	+	0	Yes	Slow	Complete	2 months	Speedy recovery after removal of tonsils and adenoids
9	+	0	No	Slow	Complete	3 months	
10	+	0	Yes	Slow	Complete	5 months	Speedy recovery after removal of tonsils and adenoids
11	+	0	No				No report
12	+	+	Yes	Speedy	Complete	3 weeks	Speedy recovery after removal of tonsils and adenoids
13	+	+	Yes	Speedy	Complete	2 weeks	Speedy recovery after removal of tonsils and adenoids
14	+	+	Yes	Speedy	Complete	1 month	Speedy recovery after removal of tonsils and adenoids
15	0	0	Yes	Speedy	Complete	3 weeks	Speedy recovery after removal of tonsils and adenoids
16	0	0	Yes	Speedy	Complete	2 weeks	Speedy recovery after removal of tonsils and adenoids
17	0	0	Yes	Speedy	Complete	1 month	Speedy recovery after removal of tonsils and adenoids

In Table 3, the treatment and results have been tabulated. In the early patients, forced feeding was given, with local treatments of the nose and throat. There were no deaths. In the later patients, little attention has been paid to feeding, the tonsils and the adenoids have been removed at once, with resulting speedy and complete recovery.

SUMMARY AND CONCLUSIONS

1. Acrodynia is a disease of infancy and early childhood, which is preceded or accompanied by an upper respiratory infection and which presents three groups of symptoms in varying degrees and combinations: (*a*) general: anorexia, loss of weight, weakness; (*b*) nervous system: hyperirritability, sleeplessness, paresthesia, anesthesia, loss of reflexes, paresis, photophobia, and (*c*) dermatologic: hyperhidrosis, miliaria, desquamation, erythema, swelling, cyanosis, coldness of hands and feet, alopecia, ulceration and loss of teeth.

2. At first the condition was erroneously thought to be a deficiency disease, but it more probably is the result of a focal infection, usually in the tonsils and the adenoids.

3. Although the dermatologic findings are pathognomonic, the disease should be suspected in cases of unexplained, persistent hyperirritability and hyperhidrosis; removal of tonsils and adenoids at this stage may abort the disease.

4. In this series, early recognition of the disorder and prompt removal of tonsils and adenoids has been followed by speedy recovery in all patients.

BLANCHING TEST IN SCARLET FEVER

USE OF A SPECIFIC STREPTOCOCCUS ANTISERUM *

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REVIEW OF THE LITERATURE

The blanching test in scarlet fever was first described in 1918. Schultz and Charlton [1] found that by injecting 1 c.c. of normal or convalescent serum intradermally into a scarlet fever patient with a fully developed eruption, the rash could be made to disappear locally. They found that this area of blanching appeared in from five to six hours; was from 1 to 2 inches (2 to 5 cm.) in diameter and persisted as long as the rash lasted. They also found that the injection of serum from a patient acutely ill with scarlet fever did not have the capacity of blanching the rash.

This observation has been confirmed by numerous observers [2] since. These investigators, however, have reported a certain number of failures. Schultz and Charlton concluded that the serum of a scarlet fever convalescent patient "recovers its lost power of blanching the rash between the fourteenth and the nineteenth day," thus assuming that their reaction is due to a normal property of human serum which is temporarily lost during the acute stage of scarlet fever, to be regained during convalescence.

It has been shown by Reymond,[3] Toomey and Nourse [4] and by others, that a small percentage of normal serums does not possess the power of blanching the rash, thus explaining the failures reported by other observers and limiting the value of the test in its negative phase. Zingher [5] found the test of greater value when used in the reverse manner—to determine whether a given rash was scarlet fever or not.

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* Received for publication, May 22, 1925.

* From the Department of Pediatrics and Infectious Diseases, University Hospital, University of Michigan.

1. Schultz, W., and Charlton, W.: Ztschr. f. Kinderh. **17**:328, 1918.

2. Paschen, E.: Dermat. Wchnschr. **68**:342, 1919. Neumann, J.: Deutsch. med. Wchnschr. **46**:566 (May 20) 1920. Schultz, W.: Acta. Med. Scandinav. **54**:492, 1921. Tron. G.: Riforma med. **37**:55 (Jan. 15) 1921; abstr., J. A. M. A. **76**:899 (March 26) 1921. Mulsow, F. W.: J. Infect. Dis. **29**:557 (Nov.) 1921.

3. Reymond, H.: Schweiz. med. Wchnschr. **51**:719 (Aug. 4) 1921; abstr., J. A. M. A. **77**:1053 (Sept. 24) 1921.

4. Toomey, J. A., and Nourse, J. D.: Extinction Tests in Scarlet Fever, Am. J. Dis. Child. **27**:95 (Feb.) 1924.

5. Zingher, A.: Proc. Soc. Exper. Biol. & Med. **21**:293, 1924.

Mair [6] suggested that the blanching was a toxin-antitoxin reaction in the skin. He found that the serum from a child, aged 5 years, did not blanch the rash of scarlet fever. Four days later she developed the disease. A sample of serum obtained on the thirty-eighth day had the capacity of blanching the rash in another case of scarlet fever.

It has previously been shown that tetanus antitoxin, sheep and rabbit serums do not blanch the rash of scarlet fever.[7] Epinephrin [7] blanches the rash at once but it returns in a few hours. It has also been shown [4] that typhoid vaccine, physiologic sodium chlorid solution, and normal horse serum do not blanch the rash. Recently, Berkhaug [8] confirmed the fact that epinephrin and normal horse serums do not blanch the rash. This investigator was also unable to produce the blanching phenomenon with diphtheria antitoxin.

Recent confirmation of the long suspected rôle played by the hemolytic streptococcus in scarlet fever [9] led Dochez and Sherman,[10] repeating the work of Marmorek,[11] of Aranson,[12] and of Moser,[13] to prepare an immune serum by injecting a horse with hemolytic streptococci over a period of six months. This serum possessed the power of blanching the rash of scarlet fever. Rashes of other diseases were not blanched by this serum.[14] They believed the reaction was antitoxic in nature, but were unable to produce an immune serum by injecting a horse with the filtrate of cultures of hemolytic streptococci. Using Dochez's and Sherman's serum, Blake [15] and his associates and Berkhaug [8] have also been able to blanch the rash of scarlet fever. Blake produced blanching in all of his thirteen cases. The serum had no effect in two cases of erysipelas. He was able to produce only very slight blanching with polyvalent streptococci serum. Berkhaugh produced blanching in forty cases of scarlet fever with Dochez' and Sherman's serum. He found that the serum failed to blanch the eruption of measles, erysipelas and rubella.

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6. Mair, W.: Lancet **2**:1390 (Dec. 29) 1923.
7. Darner, G.: Med. Klin. **17**:1543, 1921.
8. Berkhaug, K. E.: J. Clin. Invest. **1**:273, 1925.
9. Dick, G. F., and Dick, G. H.: Scarlet Fever Toxin in Preventive Immunization, J. A. M. A. **82**:544 (Feb. 16) 1924; ibid. **82**:1246 (April 19) 1924.
10. Dochez, A. R., and Sherman, L.: The Significance of Streptococcus Hemolyticus in Scarlet Fever, J. A. M. A. **82**:542 (Feb. 16) 1924.
11. Marmorek, A.: Ann de l'Inst. Pasteur 1895, p. 9593; Compt. rend Soc. de biol., 1895, p. 230.
12. Aronson, H: Berl. klin. Wchnschr. **39**:979, 1902.
13. Moser: Wien. klin. Wchnschr. **15**:1053, 1902.
14. Names of these diseases were not given by Dochez.
15. Blake, F. G.; Trask, J. D., Jr., and Lynch, J. F.: Observations on the Treatment of Scarlet Fever with Scarlatinal Antistreptococcic Serum, J. A. M. A. **82**:713 (March 1) 1924.

Dick and Dick[16] claim to have produced an antitoxic serum by injecting horses with the toxin obtained from hemolytic streptococci. They found the serum had a beneficial therapeutic effect in scarlet fever. They do not report any blanching tests with this serum.

RESULTS OF TESTS ON AUTHORS' PATIENTS

We have recently had the opportunity of carrying out the blanching test, using the globulin portion of horse serum prepared by a commercial antitoxin manufacturer for experimental purposes. This serum was prepared by injecting horses intravenously with the whole cultures of hemolytic streptococci obtained from scarlet fever cases and subcutaneously with the filtrate (toxin) of these organisms. The test was carried out by injecting 1 c.c. of the globulin solution intradermally in fifteen patients who were frankly ill with scarlet fever and showing a well marked eruption. The injection was usually made within the first forty-eight hours of the eruption. In each case a control test was used, using either convalescent scarlet fever serum or normal human serum, each of which had been shown to possess the power of blanching the scarlet fever rash. In all cases, including three done at seventy-two hours and one at ninety-six hours, blanching was secured by the antiserum. It is interesting to note that Berkhaug was unable to produce blanching with the serum of Dochez and Sherman after the eruption had lasted for sixty hours. The blanched areas were from 5 to 10 cm. in diameter, slightly irregular in shape and usually presented many radiating lines of blanching, extending into the surrounding rash for 5 to 8 cm. The areas of blanching appeared in from four to six hours, occurring slightly earlier than the areas produced by the control (convalescent and normal serums) and were slightly larger. In seven cases, a two zone reaction appeared. This consisted of a reddened area in the center of the blanched area, varying in size from 0.5 to 5 cm., which appeared earlier than the blanched area and usually disappeared before the rash faded. Berkhaug, using Dochez's and Sherman's serum, found this phenomenon to be quite rare, reporting only one occurrence in forty cases. It is possible that this is a foreign protein reaction. In no case was the erythematous area of sufficient size to obscure the area of blanching. It was noted that in all cases, except in those in which the test was carried out after the rash had lasted for seventy-two hours, the blanched areas did not desquamate.

The antiserum did not cause blanching in two cases of erysipelas. In two cases presenting a scarlatiniform eruption, the basis of which was

16. Marie, P. L.: Presse med. **29**:1001, 1921.

Case	Age	Admitted	Clinical Manifestations	Duration of Rash When Test Done, Hours	Control	1 C.c. Streptococcus Serum
1. M. B.	7	12/ 9/24	Temperature, 101 F. on admission, strawberry tongue, injected soft palate and uvula, well developed scarlatiniform eruption. Patient very ill. Desquamated in typical manner	24	1 c.c. normal human serum caused blanching of rash. Diameter of blanching 5 cm. Persisted until rash faded. Blanched area did not desquamate	Caused blanching of rash. Blanched area, 9 cm. in diameter, appeared in about 5 to 6 hours. Persisted until rash faded. Shortly after injection, a red area 0.5 cm. in diameter appeared at the site of injection and persisted for about 48 hours. Blanched area did not desquamate
2. C. D.	2	12/ 6/24	Temperature, 104 F. on admission. Very toxic, strawberry tongue, typical throat. Well developed, generalized scarlatiniform eruption. Was given 20 c.c. specific antiserum intramuscularly 12 hours after rash appeared. Twelve hours later rash had disappeared. Patient much brighter. Desquamated in typical manner	5	1 c.c. convalescent serum. Area of blanching 4 cm. in diameter. Appeared in 6 hours. Persisted until rash faded. Blanched area did not desquamate	Area of blanching appeared in 4 hours, 6 cm. in diameter. Persisted until rash faded. Blanched area did not desquamate
3. B. F.	29	12/10/24	Temperature, 103.5 F. on admission. Patient toxic. Severe sore throat. Typical strawberry tongue. Marked scarlatiniform eruption. 20 c.c. specific antiserum given intramuscularly immediately after blanching test done. Temperature dropped rapidly. Rash lasted four days. Desquamated in typical manner	12	1 c.c. normal human serum. Area of blanching, 5 cm. in diameter, appeared in 6 hours. Persisted until rash faded. Blanched area did not desquamate	Shortly after the injection a reddened area about 5 cm. in diameter appeared; at the end of 8 hours this was surrounded by a rim of blanching 1 cm. wide. The blanched area increased to 5 cm. and reddened area gradually faded. Blanched area persisted as long as rash lasted. Blanched area did not desquamate
4. A. N.	40	12/13/24	Mild sore throat. Temperature 101 F. on admission. Malaise. Uvula, soft palate and anterior pillars injected. Strawberry tongue. Desquamated in typical manner. Patient also had diabetes mellitus.	72	1 c.c. convalescent serum. Area of blanching, size 5 cm., appeared in 6 hours. Persisted as long as rash lasted. Fine powdery desquamation in blanched area occurred	Small red area 1 cm. in diameter appeared in 2 hours; at end of 6 hours it was surrounded by a blanched area; total diameter 3 cm. Blanched area and reddened area in its center persisted until rash faded. Fine powdery desquamation occured in blanched area
5. A. N.	24	12/15/24	Severe headache, backache, malaise, sore throat. Temperature, 101 F. on admission. Soft palate, uvula and anterior pillars markedly injected. Strawberry tongue. Well developed scarlatiniform eruption. Desquamated in typical manner	24	1 c.c. normal human serum. Area of blanching, 5 cm. in diameter, appeared in 6 hours. Persisted until rash faded. Blanched area did not desquamate	Area of blanching 9 cm. in diameter, in center of which there appeared, early, a reddened area 1 cm. in diameter which faded before rash did. Blanched area did not desquamate
6. E. B.	21	12/21/24	Headache, malaise, sore throat. Temperature 102 F. on admission. Moderately toxic. Markedly injected soft palate, uvula and anterior pillars. Strawberry tongue. General scarlatiniform eruption. Desquamated in typical manner	18	1 c.c. normal human serum. Area of blanching, 5 cm. in diameter, appeared in 6 hours. Persisted until rash faded. Blanched area did not desquamate	Area of blanching, 9 cm. in diameter, appeared in 5 hours. Persisted until rash faded. Blanched area did not desquamate
7. S. F.	5	12/30/24	Sore throat. Temperature 102.5 F. on admission. Moderately ill. Soft palate and uvula and anterior pillars injected. Strawberry tongue. Generalized scarlatiniform eruption. Desquamated in typical manner	72	1 c.c. normal human serum. Area of blanching, 5 cm. in diameter, appeared in 6 hours. Lasted until rash faded. Blanched area showed faint desquamation	Area of blanching, 6 cm. in diameter, appeared in 5 hours. Lasted as long as rash persisted. Blanched area showed faint desquamation

8. K K.	14	12/30/24	Sore throat. Quite toxic. Temperature, 104 F. on admission. Markedly injected soft palate, uvula and anterior pillars. Mucopurulent exudate in nasopharynx. Strawberry tongue, generalized eruption (scarlatiniform). Desquamated in typical manner	24	1 c.c. normal human serum. Area of blanching, 5 cm. in diameter, appeared in 6 hours. Lasted as long as rash persisted. Blanched area did not desquamate	Area of blanching, 9 cm. in diameter, appeared in 5 to 6 hours. Persisted as long as rash lasted. Blanched area did not desquamate
9. L. H.	25	1/ 9/25	Sore throat, headache, malaise. Temperature 102.5 F. on admission. Strawberry tongue; soft palate, uvula, anterior pillars and pharynx markedly injected. Exudate on tonsils. Not very ill. Generalized scarlatiniform eruption which faded in 36 hours. Slight desquamation of finger tips only	12	1 c.c. normal human serum. Area of blanching, 3 cm. in diameter, appeared in 6 hours. Persisted as long as rash lasted. Slight desquamation on finger tips only	An area of redness, 1 cm. in diameter, appeared in 3 hours; in 6 hours this was surrounded by a rim of blanching 2.5 cm. wide which persisted as long as rash lasted. Slight desquamation on finger tips only
10. D. C.	25	1/13/25	Sore throat, headache, backache, malaise. Temperature, 100 F. on admission, not toxic. Marked injection of soft palate, uvula and anterior pillars. Exudate on tonsils. Strawberry tongue. General scarlatiniform eruption. Desquamated in typical manner	12	1 c.c. normal human serum. Area of blanching, 5 cm. in diameter, appeared in 6 hours. Persisted as long as rash lasted. Blanched area did not desquamate	Area of blanching, 10 cm. in diameter, appeared in 5 hours. Persisted as long as rash lasted. There was a red area in center, 2.5 cm. in diameter, which appeared in 2 hours and disappeared in 48 hours. Blanched area did not desquamate
11. B. H.	26	2/ 6/25	Sore throat, severe joint pains. Temperature, 102 F. on onset. Strawberry tongue; soft palate, uvula, anterior pillars and pharynx markedly injected. Exudate on tonsils. Moderately ill. Very marked scarlatiniform eruption with vesiculation. Very marked desquamation	96	1 c.c. normal human serum. Area of blanching, 5 cm. in diameter, appeared in 6 hours. Persisted as long as rash lasted. Slight desquamation in blanched area	Area of blanching, 7 cm. in diameter, appeared in 5 to 6 hours. Area of redness in center, 1 cm. in diameter. Persisted as long as rash lasted. Slight desquamation in blanched area
12. C. L.	3	2/24/25	Temperature, 100 F. Typical throat with exudate on tonsils. Strawberry tongue. Generalized scarlatiniform eruption. Patient not very ill. Desquamated in typical manner	72	1 c.c. normal human serum. Area of blanching appeared in 7 hours, 3 cm. in diameter. Persisted as long as rash lasted. Blanched area showed slight desquamation	Blanched area appeared in 6 hours, 4 cm. in diameter. Persisted as long as rash lasted. Blanched area did not desquamate
13. J. R.	23	2/25/25	Headache, sore throat, malaise, chill and vomiting. Temperature, 103 F. Severely ill. Strawberry tongue, typical throat. Generalized scarlatiniform eruption. Was given 20 c.c. specific antiserum intramuscularly on admission. Patient desquamated slightly on finger tips only	36	1 c.c. normal human serum. Area of blanching, 5 cm. in diameter, appeared in 6 hours. Persisted as long as rash lasted. No desquamation occurred except on finger tips	Area of blanching, 5 cm. in diameter, appeared in 5 hours. Reddened area in center, 0.5 cm. in diameter. Persisted as long as rash lasted. No desquamation occurred except on finger tips
14. W. S.	24	3/25/25	Headache, sore throat, malaise. Temperature, 103 F. Strawberry tongue. Soft palate, uvula, anterior pillars and pharynx markedly injected. Moderately ill. Generalized scarlatiniform uniform eruption. Desquamated in typical manner	24	1 c.c. normal human serum. Area of blanching, 5 cm. in diameter, appeared in 6 to 7 hours. Persisted as long as rash lasted. Blanched area did not desquamate	Area of blanching, 7 cm. in diameter, appeared in 7 hours. Persisted as long as rash lasted. Blanched area did not desquamate
15. C. A.	5	4/20/25	Temperature, 102 F. Typical throat. Strawberry tongue. Not very ill. Generalized scarlatiniform eruption. Patient desquamated in typical manner	24	1 c.c. normal human serum. Area of blanching, 5 cm. in diameter, appeared in 6 to 7 hours. Persisted as long as rash lasted. Blanched area did not desquamate	Area of blanching, 6 cm. in diameter, appeared in six hours. Persisted as long as rash lasted. Blanched area did not desquamate

fundamentally anaphylactic, one case being due to a food sensitization, the other to a boil, we were also unable to produce the blanching phenomenon.

In three cases of scarlet fever with a definite eruption, the intradermal injection of diphtheria antitoxin was essentially negative.

COMMENT

The results of this small series would seem to indicate that the specific antiserum used possesses definite antibodies for scarlet fever. Enough data on the therapeutic use of this antiserum have not been collected to warrant a report on this aspect.

On account of the greater difficulty in obtaining normal or convalescent serum for the blanching test, it appears that a specific antiserum would fill a practical need in the diagnosis of scarlet fever.

SUMMARY

In fifteen cases in which it was tried, an antiserum prepared by injecting horses with the cultures and filtrate of hemolytic streptococci obtained from cases of scarlet fever was effective in producing the Schultz-Charlton blanching phenomenon.

The antiserum was not effective in blanching the eruption of two cases of erysipelas and of two cases presenting a scarlatiniform eruption on an anaphylactic basis.

In three cases we were unable to blanch the rash of scarlet fever by using diphtheria antitoxin.

AN APPARATUS FOR THE RAPID PREPARATION OF PROTEIN MILK*

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Protein milk consists of a quart of buttermilk, or of a pint of buttermilk and a pint of water, in which is mixed the drained curd from a quart of whole milk. The curd is usually prepared by adding one half ounce of liquid rennet to 1 quart of whole milk, heating to 100 F., allowing the mixture to stand until clotted (usually fifteen minutes) and pouring the semisolid coagulum into a cheesecloth bag which is then suspended until the whey drains away (about two hours). The drained curd is usually

Apparatus for the rapid preparation of protein milk.

then finely divided by forcing it with a wooden potato masher or a large spoon through cheesecloth spread over a sieve. The same proportions are used in preparing larger amounts.

During the summer months, when several gallons of protein milk are used daily in children's hospitals, this process requires several hours of arduous labor. Several mechanical devices have been made to break up the milk curd sufficiently so that the protein milk will be an homogeneous suspension containing finely divided particles. An apparatus which has proved to be satisfactory for the last two years is illustrated here. It consists of a heavy seamless steel cylinder, 20 inches (50 cm.) long by 6 inches (15 cm.) in diameter, mounted on three wheels with 5 feet of

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* From the Department of Pediatrics, and the Harriet Lane Home, Johns Hopkins Hospital.

hose fitted to an opening in the bottom of the cylinder. The capacity is 2½ gallons. The head is equipped with gears and a crank which operate a leather covered piston provided with an expansion ring which prevents leakage. This apparatus is sold for $36 by the Ekern-Turk Manufacturing Company, Pipestone, Minn., for the purpose of forcing thick lubricating grease into automobile gears. By removing the hose from the base, mounting the apparatus on a wooden support 14 inches (35 cm.) high, and placing a bucket underneath, it can readily be adapted to the rapid preparation of protein milk. Two disks of 16 gage brass wire screen (12 wires to the inch) 6 inches in diameter with two layers of cheesecloth between them are placed in the bottom of the cylinder. The apparatus is then cleansed by pouring boiling water over the piston and into the cylinder from which it escapes through the hole at the bottom into the bucket underneath. The drained milk curd from the cheesecloth bags is then placed in the cylinder, the piston is swung into place and the pressure commenced by turning the crank. As soon as all of the whey has been forced through the opening at the bottom of the cylinder and the finely divided curd appears, the bucket is replaced by a clean container. The pressure is then increased until all of the curd has been forced out of the cylinder. Having passed through two layers of wire screen and two layers of cheesecloth, the curd is so finely divided that it forms an homogeneous suspension when mixed with buttermilk or with buttermilk and water. One gallon of curd can be broken up with slight effort in ten minutes. If used daily, the wire screen should be renewed every four or six months, and the leather cover for the piston every year.

The ordinary hand grease gun can be advantageously used in making small amounts of protein milk.

PROGRESS IN PEDIATRICS

ICTERUS NEONATORUM *

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DIAGNOSIS

Among the many varieties of jaundice, icterus neonatorum has occupied a peculiar place for many years. It is a variety of jaundice which nearly always has a favorable progress, and as a rule many phenomena which we see, almost without exception, in other forms of jaundice are lacking here. The majority of writers are inclined to regard icterus neonatorum as a physiologic phenomenon, a view which may be justified by the fact that this condition is so often noted. Though the reports of different writers do not quite agree in this respect, at present about 80 per cent. of them do. Almost without exception, premature and weak children have icterus neonatorum more frequently than do normal children; it is said that boys are more commonly affected than girls.[1]

With this form of icterus, as before mentioned, many phenomena are lacking which are seen in the other forms. Among these are: a special distribution of the icteric color of the skin, together with an absence of the yellow color of the sclerae; absence of dissolved bile pigments in the urine; absence of clay colored feces; absence of slowing of the pulse and an increase of the temperature. If a new-born infant with icterus neonatorum dies, changes appear at necropsy which as a rule are not found with the usual forms of icterus. There is a general icterus of the tissues, but the striking feature is that the yellow color in the kidneys, spleen and more especially in the liver is very faint. The bile ducts themselves are normal. Although some writers suggest[2] that with icterus neonatorum there should be strong icteric color of the large nuclei of the brain and of the medulla, that is, a so-called "Kernicterus,"[3] this is not so. On the contrary, according to Beneke,[4] a yellow color

* Received for publication, July 8, 1925.

1. Steven, J. L.: Glasgow M. J. **47**:4, 1897. Hilgenberg, F. C.: Monatschr. f. Geburtsh. u. Gynäk. **68**:326, 1925.

2. Rolleston, Humphrey: Jaundice in the New-Born, Oxford Med. **3**:320, 1920. Aschoff, L.: Lehrbuch der pathologischen Anatomie, Ed. 4, 1, 464.

3. Schmorl: Verhandl. d. deutsch. path. Gesellsch., p. 109, 1904.

4. Beneke: Kernikterus der Neugeborenen, München. med. Wchnschr., p. 2023, 1907. Hart, C.: Über den Kernikterus der Neugeborenen, Berl. Klin. Wchnschr. **54**:71, 1917. Hall, H. C.: La dégénérescence hépatolenticulaire, Paris, 1921, p. 334.

of the before-mentioned parts of the central nervous system is not seen, even in those cases of severe icterus neonatorum which come to necropsy. The "Kernicterus" belongs, according to Beneke and other writers, to a definite variety of icterus gravis of the new-born, which in the cases described showed a familial character.

ETIOLOGY

The opinions on the origin of icterus neonatorum are very different, and as will appear from what follows, are quite contradictory. Still it is possible to arrange the conceptions formed by a large number of writers on the ground of a great many researches, so that the writers can be divided chiefly into five groups, according to their conceptions of the cause of icterus neonatorum:

Group 1.—To the first group belong the research workers, according to whom the origin of icterus neonatorum in a more or less modified form is explained by a theory proposed many years ago by Quincke.[5] According to this writer, icterus neonatorum arises from the fact that the ductus venosus arantii, the direct communication between the vena umbilicalis and the vena cava inferior, which is formed in the later period of embryonal life, remains open for some days after birth. The bile pigments, which, according to Quincke, are present in the meconium in large quantities and are resorbed by the intestinal canal, pass now through the open ductus venosus arantii directly into the general circulation, which thus becomes overcharged with bile pigments.

Group 2.—The second group of writers, following the methods of Ylppö and Ada Hirsch, regard icterus neonatorum as due to an insufficient functioning of the liver, as other organs of new-born infants also are supposed to have an inferior functioning (that is, the kidneys; there is always a trace of albumin and sugar in the urine of new-born infants). The researches of Ylppö [6] and Hirsch,[7] published in 1913, furnish exact quantitative estimations of the content of bile pigments of the blood in the umbilical cord and of the circulating blood of new-born infants. These researches indicated that in all new-born infants, even in those without icterus neonatorum, we have to deal with a bilirubinemia, which increases in the first days after birth. If the quantity of

5. Quincke, H.: Über die Entstehung der Gelbsucht der Neugeborenen, Arch. f. exper. Path. **19**, 1885.

6. Ylppö, Arvo: Icterus neonatorum (inkl. I. n. gravis) und Gallenfarbstoffsekretion beim Foetus und Neugeborenen; Quantitative (spektrophotometrische) Studien über das Verhalten des Gallenfarbstoffes im fötalen und Neugeborenen Organismus, Ztschr. f. Kinderh. **9**:208 (Dec.) 1913; ibid. Ikterus Neonatorum, Ergebnisse der ges. Medizin **5**, 1924.

7. Hirsch, Ada: Die physiologische Ikterusbereitschaft des Neugeborenen, Ztschr. f. Kinderh. **9**:196 (Dec.) 1913.

bile pigments in the blood exceeds a certain limit, then icterus of the skin appears. The cause of the bilirubinemia (and so indirectly of icterus neonatorum) must be sought in the insufficient function of the liver. For this reason the liver permits the bile pigments to enter the general circulation, as every fetal liver does.

Group 3.—An older theory, which of late has found only a few defenders, explains the cause of icterus neonatorum as due to infection. In consequence, in an infectious intestinal catarrh, inflammation of the bile ducts appears, with occlusion of the ductus choledochus.

Group 4.—The fourth group, in which we must reckon some of the most recent writers, accepts a relation between the appearance of icterus neonatorum and an increased destruction of the blood. In this conception too much bilirubin is found in the body of the new-born either in the liver or beginning before birth.

Group 5.—The Vienna pediatrician, Schick,[8] some years ago proffered the theory that icterus neonatorum should be looked on as a consequence of an increased destruction of the maternal blood.

I shall now review briefly these researches, more especially those done since 1913, when Ylppö and Ada Hirsch published their investigations, which in more ways than one have renewed interest in this problem. In this, I shall refer chiefly to the mild forms of icterus neonatorum; the rare severe varieties of icterus neonatorum and the question of their possible mutual relationship being discussed later.

FIRST GROUP

I. The theory of Quincke, which for a long time has had a large number of adherents, had been disputed on several grounds. Knöpfelmacher[9] pointed out that icterus neonatorum was not prevented if immediately after birth the intestinal canal was freed from meconium by high clysmas of acidified water, in which bilirubin is insoluble. Nor is the appearance of icterus prevented by the escape of the meconium in utero or during birth, as was shown by Kehrer[10] as early as 1871. Further, it was found by Ylppö, that the meconium contains remarkably few bile pigments, and that these consist chiefly of biliverdin, whereas in the blood of icteric children only bilirubin can be demonstrated. The changes found in the ductus venosus arantii at the necropsy of new-

8. Schick, B.: Der Icterus neonatorum als Folge des Abbaues mütterlichen Blutes, Ztschr. f. Kinderh. **27**:231, 1921.

9. Knöpfelmacher, W.: Die Ätilogie des Icterus neonatorum, Jahrb. f. Kinderh. **67**:1 (Jan.) 1908.

10. Kehrer: Studien über den Icterus neonatorum, Österreich, Jahrb. f. Kinderh. **88**:71, 1871.

born infants who died during the first days of life were such that the possibility could be excluded that after the birth blood could have passed by this way.

Contrary to these objections, however, some good arguments have appeared, which speak for the fact that the bile pigments may be reabsorbed from the intestinal canal. These arguments are chiefly of a histologic nature. Aschoff [11] established the absorption of bile pigments from the intestine of the fetus by showing the presence of meconium cells in the epithelium of the lower part of the ileum. Von Möllendorff [12] found, in the intestine of new-born mice brown granules and bodies which, according to him and in agreement with Aschoff were resorbed bile pigments. In thirty human cases of fetuses, premature and new-born infants, Bohnen [13] obtained analogous results, and concluded from his histologic and michrochemical results that the bile pigments are resorbed in the whole intestinal canal, but more especially in the lower part of the ileum. There are two possibilities. First: the bile pigments may fail to reach the liver directly, if the ductus venosus arantii is patent. Second: the liver may be unable to retain the bile pigments when a certain degree of bilirubinemia is reached, in analogy with what is supposed to happen in alimentary glycosuria. If food is taken, the resorptive function of the intestine increases and then the resorbed bile pigments accumulated in the intestinal epithelium will first enter the circulation. Then the accumulation of bile pigments in the skin would still be favored by loss of water in the new-born infants and perhaps also by an increased breaking down of red blood corpuscles. The loss of water would cause a decrease of the quantity of blood and so indirectly an increased concentration of its contents of bilirubin. In this connection we may point to the results of the estimations of the refractive index of the serum, done by Foncin [14] in a small number of new-born infants. During the physiologic decrease of weight in non-icteric children, Foncin found a decrease of the refraction index, whereas the icteric new-born infants showed an increase. This increase of the refractive index was larger than could be caused by admixture with bile substances.

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11. Aschoff, L.: Lehrbuch der pathol. Anatomie, Ed. 5, p. 793.

12. Von Möllendorff, W. L.: Über die Auteilnahme des Darmepithels an der Verarbeitung enteral und perenteral zugeführter saurer Farbstoffe, München. med. Wchnschr. **71**:569, 1924.

13. Bohnen, P.: Histologische Untersuchungen über Gallenfarbstoffresorbtion im Säuglingdarm, Klin. Wchnschr. **3**:1993 (Oct. 20) 1924.

14. Foncin, R.: Études refractométrics du sérum du nouveau-né normal et du nouveau-né ictérique, Compt. rend. Soc. de biol. **89**:583, 1923.

Retzlaff [15] declares himself in favor of the theory of Quincke, on the ground that he found bilirubin in the lymph of the thoracic duct. De Micheli [16] agrees with him on the grounds of his own researches, but, in addition, he supposes that icterus neonatorum will appear only when the hyperbilirubinemia, which exists in all new-born infants, does not decrease within twenty-four hours after birth.

Eppinger,[17] who claims to have no clinical experience with icterus neonatorum, but only a pathologic-anatomic one, is a supporter of the theory of Quincke. He thinks that there must be a large deposit of bile pigments in the meconium, but regards cooperation of the ductus venosus arantii as superfluous. On the contrary, he believes the reticulo-endothelial apparatus to be relatively insufficient, in this case more especially the "Sternzellen" of Kupffer, in which organ, according to Eppinger, Lepehne and others, the bile pigments are formed. On account of this insufficiency, the bile absorbed from the intestine would enter the circulation. In addition to this, there would be a sufficient quantity of bile pigments excreted by way of the bile ducts. According to Eppinger, the absorption from the intestinal tract could begin immediately before birth, so that it could be possible that, although Knöpfelmacher has removed the greater part of the meconium from the intestine by his high clysmas, a sufficient quantity of bile from the meconium has been resorbed before birth. Eppinger emphatically denies icterus neonatorum to be mechanical on the ground of pathologic-anatomic statements; this statement will be referred to later.

SECOND GROUP

2. The researches of Ylppö and Ada Hirsch showed quite clearly that the presence of bile pigments in the blood of the new-born child should be looked on as being quite physiologic. By these researches, as Finkelstein [18] and others remark, the problem of icterus neonatorum is chiefly reduced to the question of why the quantity of bile pigments entering the circulation of new-born infants differs in various children. Ylppö explains this fact by a functional immaturity of the liver of the new-born infant. As we live in a period when functional investigation of all organs is of general interest, it is easily understood that the explanation of Ylppö will be readily accepted and also that it has been the direct cause of a large number of experimental investigations, which,

15. Retzlaff: Experimentelle und klinische Beiträge zur Pathologie des Ikterus, Ztschr. f. d. ges. exper. Med. **34**:133, 1924.

16. De Micheli, E.: Studi sulla bilirubinemia, Arch. di patol. e clin. med. **3**:42, 1924.

17. Eppinger, H.: Der Ikterus, in Handbuch der speziellen Pathologie und Therapie innerer Krankheiten, IV, second half, **3**, 1923.

18. Finkelstein, H.: Lehrbuch der Säuglingskrankheiten, Ed. 3, Berlin, 1924.

however, have given contradictory results. It may be said beforehand, that various workers [19] have been able to confirm substantially the results of Ylppö and Ada Hirsch.

Whether the cause of icterus neonatorum may be sought in an insufficient function of the liver has been tested by doing a series of different experiments with new-born children, under the name of liver function experiments. Thus, Heynemann [20] performed the functional test with levulose, from which he concluded that there was an insufficient function of the liver. Linzenmeier and Lilienthal [21] examined the proteopexic function of the liver of new-born infants after the method of Widal. In icteric children especially, they found obvious leukopenia after breast feeding. From this they concluded that there must be a definite relation between icterus neonatorum and liver insufficiency, as from the positive reaction of Widal they could nearly predict with certainty the appearance of icterus neonatorum. These researches have been repeated by different workers, but could not be confirmed. On the contrary, Hainiss and Heller [22] found just the opposite in icteric new-born infants, more often a negative than a positive result of the reaction. It is true that Linzenmeier and Ivänyi [23] maintained their former opinion in the face of this criticism, but later researches of Simon and Wellewa [24] and of Joseph and Guskar [25] have also given contrary results. The former investigators found leukopenia, followed by icterus, in half of the subjects to whom tea was given as the first food, and in the other half they found leukocytosis but no icterus. It is difficult to suppose that the cause of the leukopenia was stimulation caused by albumin which had been split insufficiently and which had passed through a deficiently functioning liver. This last idea would be in agreement with the ideas of those who do not look on the "crise hemoclasique" of Widal as being a specific albumin reaction, and who deny its significance as a liver function test. Perhaps in the near future we shall get better proofs

19. Meyer and Adler: Über den Bilirubinstoffwechsel vei Neugeborenen; Ein Beitrag zur Frage des Icterus neonatorum, Zentralbl. f. Gynäk. **48**:1514, 1924.

20. Heynemann, T.: Die Entstehung des Ikterus neonatorum, Zentralbl. f. Geburtsch. u. Gynäk. **76**:788, 1915.

21. Linzenmeier, G., and Lilienthal: Zur Frage des Icterus neonatorum, Zentralbl. f. Gynäk. **46**:1873, 1922.

22. Hainiss, E., and Heller, S.: Icterus neonatorum und hämoklasische Krise, Zentralbl. f. Gynäk. **47**:1801 (Dec. 1) 1923. Maroudis, G.: Zur Frage des Ikterus neonatorum und der Widalschen Reaktion, Zentralbl. f. Gynäk. **48**:275 (Dec.) 1924.

23. Linzenmeier, G., and Ivänyi, F.: Icterus neonatorum und Widalschen Reaktion, Zentralbl. f. Gynäk. **47**:1805 (Dec. 1) 1923.

24. Simon, W., and Wellewa, Z.: Icterus neonatorum und Widalschen Reaktion, Zentralbl. f. Gynäk. **48**:1250 (June 7) 1924.

25. Joseph and Guskar: Zur Frage des Ikterus neonatorum und der Widalschen Reaktion, Klin. Wchnschr. **3**:2247 (Dec. 2) 1924.

for the truth of the doctrine that the cause of icterus neonatorum must be sought in the functional immaturity of the liver, by a thorough physico-chemical analysis of the blood. Recently more attention has been paid to this, more especially with regard to a new functional liver diagnosis of adults. Already György,[26] and Duzar and Rusznyak [27] have been able, on the basis of such physiochemical analysis, to delimit a physiologic new-born period, which is the period of the first 6 to 8 weeks. Duzar and Rusznyak think that the changes in the protein fractions of the plasma play the principal rôle in this period, whereas György ascribes the principal rôle to the lipoid content of the plasma.

Meier,[28] on the ground of his observations with animals, has declared himself in favor of explaining icterus neonatorum as due to a physiologic immaturity of the liver. With new-born dogs he found a physiologic icterus neonatorum, which could not be increased by injection of phenylhydrazin in quantities as large as could possibly be given. On this ground he denies the importance of the destruction of blood for the appearance of icterus neonatorum, which he explains by an insufficient liver function.

Rosenthal, Kleeman and Nossen [29] are of the opinion that the theory of the functional immaturity of the liver of new-born infants may be supported by a fact, established previously by Laveran and later on by themselves, namely, that the serum of new-born infants has only slight power to kill trypanosomes. Though it looks as if the study of the trypanosidic properties of the serum promises to become of great value for judging the liver function, we have, in special cases of icterus neonatorum, to wait for further investigations of new-born infants, comparing those who have icterus with those who have not.

Cserna [30] has joined the supporters of the theory of insufficient liver function on quite different grounds. After tying the umbilical cord, he takes blood from the still pulsating stump and from the placental stump. Then he determines the content of bile pigments and finds an average of 25 per cent. more bile pigments in the blood of the stump than in that

26. György, P.: Über den Lipoidgehalt des Nabelschnurblutserums und des mütterlichen Blutserums, Klin. Wchnschr. **3**:483 (March 18) 1924. Fuhrmann, L., and Kisch, Bruno: Vergleichende Blutuntersuchungen bei Mutter und Neugeborenen. Beobachtungen über Oberflächenspannung des Serums und Hämolyse, Ztschr. f. d. ges. exper. Med. **24**:84, 1921. Hornung: Klin. Wchnschr. **4**:75, 1925.

27. Duzar, J., and Rusznyak, S.: Monatschr. f. Kinderh. **28**:25, 1924.

28. Meier, K.: Icterus Neonatorum, Monatschr. f. Geburtsch. u. Gynäk. **66**:337, 1924. Beyers, J. A.: Urobilinurie en icterus by onze plantenetende huisdieren, dissert. Utrecht, 1923.

29. Rosenthal, F.: Die trypanociden Stoffe des menschlichen Serums, ihre biologische und klinische Bedeutung, Klin. Wchnschr. **3**:1659 (Sept. 9) 1924.

30. Cserna, S., and Liebmann, S.: Beitrag zur Lehre des Icterus neonatorum, Klin. Wchnschr. **2**:2122 (Nov. 12) 1923.

of the placenta. In connection with this he says that the bile pigments formed during intra-uterine life by the destruction of blood are excreted from the blood by the placenta. Therefore, every new-born infant should have a latent dynamic icterus at the moment of its birth, for so far as the excretion of bile pigments is concerned, the function of the placenta would be less than the function of the liver. Immediately after birth the liver would perform this function; when this function is insufficiently developed at birth, the consequence would be a manifest icterus.

When confirmed, these researches may be looked on as being of great importance, but before confirmation, some objections may be raised to them. According to a great many workers, including those of earlier periods, the placenta as a rule is not permeable to bile pigments. Concerning the passage of bile pigments through the placenta from the maternal blood into the blood of the umbilical cord, clinical observation teaches us the same thing, as Ylppö remarks, for icteric mothers may give birth to nonicteric children. Then we should expect, according to the conception of Cserna, that if ligation of the umbilical cord has been delayed, the icterus would be caused less easily. But experience, if it does not prove the contrary, does not speak in favor of this.[31]

Notwithstanding manifold contradictions, the theory of Ylppö has been accepted by many workers. So far as other factors are considered, the functional immaturity of the liver is also often held responsible in addition to those other factors. Among workers who of late years have ascribed a preponderating significance to this insufficient liver function as the cause of the icterus neonatorum, may be mentioned: Ibrahim,[32] Zamorani,[33] Looft [34] and Von Reuss.[35] Hess [36] looks on icterus neonatorum as due to a disproportion between excretion and secretion of bile.

THIRD GROUP

3. To those who explain the cause of icterus neonatorum as due to infection, belong, among others, Quisling,[37] Czerny and Keller [38] and

31. Affanassiew, H.: Über Icterus und Hämoglobinurie, hervorgerufen durch Foleylendianmin und anders Blutkör, perchenzerstörende Agentien, Ztschr. f. klin. Med. **6**:281, 1883.

32. Ibrahim, J.: Krankheiten der Neugeborenen, Handb. d. Geburtsh. **3**:787, 1920.

33. Zamorani: Le più recenti vedute sulla bilirubinogenesi in rapporto coll'ittero dei neonati, Riv. di clin. pediat. **21**:385, 1923.

34. Looft, C.: Icterus neonatorum, Med. Rev., Bergen **36**:375, 1919.

35. Von Reuss, A.: Einige Bemerkungen uber die Bedeutung der während der Geburt eintretenden Zirkulationsströrungen fur das Kind, Gynäk. Rundsch. **9**:1, 1915.

36. Hess, A. F.: The Secretion of Bile in Icterus Neonatorum, Am. J. Dis. Child. **11**:294 (April) 1916.

37. Quisling, N. A.: Klinische Studien über icterus neonatorum, Arch. f. Kinderh. **17**:32, 1895.

38. Czerny and Keller: Des Kindes Ernährung, etc., Leipzig, Wien., 1901-1912.

Unger.[39] Of late years also, Herzfeld [40] has declared himself in favor of this theory, which, as has been remarked, has at present only few adherents. According to this theory, in consequence of an infectious intestinal catarrh, a swelling of the ductus choledochus appears, followed by an obstructive icterus. To the defenders of this theory Opitz [41] may be reckoned; he mentions an obstructive icterus, caused by swelling of the duodenal mucosa. Czerny and Keller found support for the theory in two facts: first, in the parallelism which they have established between the frequency of icterus neonatorum and the frequency of puerperal infection, and secondly, in the decrease of the frequency of icterus neonatorum together with the improvement of antiseptic measures. On account of this, Unger has declared that they have succeeded, owing to excellent hygienic methods, in diminishing the frequency of icterus neonatorum to 20 per cent. in Vienna. Undoubtedly this figure is much too low, as Ylppö, who made a statistical study in a large clinic in Berlin, where only women who were free from infectious diseases were admitted, reached a figure of 82 per cent., which is more in agreement with the current figures. He ascribes the low figures found in Vienna to the fact that apparently the light cases of icterus neonatorum were not taken into account in preparing the statistics. However, the question of the frequency of icterus neonatorum is rather without importance, as Ylppö rightly says.

Herzfeld explains icterus neonatorum as due to an infection acquired during birth. It is not a physiologic icterus, but an icterus caused by aspiration, so that weak children are more susceptible to it. He finds support for this theory in his observation, that icterus neonatorum appeared less frequently if immediately after birth the mucus was sucked out of the mouth by aid of a soft catheter.

In this connection the theory, dating from the pre-aseptic period, may be recalled, that icterus neonatorum is favored by exposure to cold. It was thought then that cold increased the chances of infection.[42] Modern workers, who consider cooling of significance in causing icterus neonatorum, either do not give any explanation of this effect, or they give a different one (Meyer and Adler,[43] Leuret [44]).

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39. Unger: Beiträge zur Pathologie und Klinik der Neugeborenen: Icterus neonatorum, Ztschr. f. Kinderh. **5**:312, 1912.

40. Herzfeld, B.: Das neugeborene Kind und seine Eigentumlichkeiten, Jahrb. f. Kinderh. **99**:75, 1922.

41. Opitz: Zur Physiologie der Milchsekretion und der Ernährung das Neugeborenen in den ersten Tagen, Med. Klin. **39**:1483, 1911.

42. Legg, Wickham: Bile Jaundice and Bilious Diseases, London, 1879, p. 623.

43. Meyer and Adler: Footnote 19.

44. Leuret: Arch. d. med. d. enf., 1905, p. 129.

As an argument against the theory that icterus neonatorum can be explained as an infectious icterus, it has been repeatedly remarked that the form of icterus which is considered to have an infectious cause, namely, catarrhal icterus, does not occur or only rarely occurs in the first years of life,[45] though children of this age often suffer from severe catarrhs of the intestinal canal (Reusz[46]). That icterus neonatorum cannot be looked on as a mechanical icterus, as the infectious theory assumes (Hasse[47]), may be proved not only by the fact that the feces are not clay colored, but also by the result of the histologic examination of the liver. This examination has been made by Eppinger;[48] later by Abramow and Knöpfelmacher[49] with the same results. Eppinger, by using his method of bile capillaries, found neither dilatation nor tearing of the bile capillaries, which changes would be, according to him, characteristic of obstructive icterus.

FOURTH GROUP

4. After the researches of Hymans van den Bergh and Snapper,[50] it seemed possible to make a sharper differentiation between obstructive icterus and the other forms of icterus which are caused by increased blood destruction. It is obvious that the results of these researches would be used in obtaining more accurate information regarding icterus neonatorum. Lepehne,[51] in analyzing the blood of new-born infants, found that the serum showed only the indirect diazoreaction. That is, the serum albumin first has to be precipitated with alcohol, before the addition of the diazoreagent causes the diazobilirubin to appear. For this reason Lepehne thought himself justified in assuming a relationship between icterus neonatorum and excessive hemolysis, so that it might be classed with hemolytic icterus, as had been done previously by other investigators.[52] Indeed, icterus neonatorum does agree in many points with hemolytic icterus; thus, for instance there is an absence of stenosis of the bile ducts and of clay colored feces, also there is little or no bile pigment in the urine. A further argument for excessive hemolysis is the fact that later on Lepehne was able to analyze in a number of cases the duodenal fluid of new-born infants, just as A. F. Hess[53] had done,

45. Neumann: Deutsch. med. Wchnschr., 1899, p. 574.
46. Reusz: Krankheiten der Neugeborenen, Berlin, 1914, p. 47.
47. Hasse, C.: Der Icterus neonatorum, Jahrb. f. Kinderh. **69** (June) 1909.
48. Eppinger: Footnote 17.
49. Knöpfelmacher, W.: Die Entstehung des Ikterus neonatorum, Wien. med. Wchnschr. **57**:922, 1907.
50. Hymans van den Bergh, A. A.: Der Gallenfarbstoff im Blute, Leiden.
51. Lepehne: Pathog. d. Ikterus, 1918, Ergebn. d. ges. inn. Med. u. Kinderh. **20**:221, 1921; Zur Kenntniss des icterus neonatorum, Monatschr. f. Geburtsch. u. Gynäk. **60**:277, 1922.
52. Leuret: Footnote 44.
53. Hess, A. F.: A Study of Icterus Neonatorum by Means of the Duodenal Catheter, Am. J. Dis. Child. **3**:304 (May) 1912.

and that he found there much bile pigment. However, between icteric and nonicteric children no definite differences could be observed.

A great many other investigators supported the theory of Lepehne on different grounds or used the same method to determine the anhepatic character of the bilirubin in new-born infants (Knöpfelmacher and Kohn,[54] Rolleston,[55] Snapper,[56] Pollitzer,[57] Williamson,[58] Schiff and Färber,[59] Decio,[60] Kraus [61] and Beyers.[62]). In this connection we also may mention the names of Gessner [63] and Luska.[64] The latter explains the appearance of icterus neonatorum by an excessive hemolysis, which, however, would occur only under pathologic conditions. This hemolysis he supposed to be caused by toxins of hemolytic staphylococcus. Luska is said to have succeeded in culturing these staphylococci from feces, blood, wounds of the navel and from the contents of pemphigus-blebs. The former (Gessner) looks on icterus neonatorum as a pathologic process, purely hematogenic, in which an acquired "culturschaden" of the human skin would play an important rôle and would also be an explanation of its frequency.

As the before-mentioned investigators bare their opinions on the result of the reaction of Hymans van den Bergh, the following remark may be made. The results of recent investigations [65] seem to justify us in saying that we should not attribute as great significance as formerly to the result of this diazoreaction in explaining the cause of icterus neonatorum. Thus the explanation of icterus neonatorum on the ground of the result of this reaction certainly loses much in value.

The comparison of icterus neonatorum with as clearly defined a disease as hemolytic icterus, has, furthermore, lost part of its value by the results of the investigation of other symptoms which are common

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54. Knöpfelmacher, W., and Kohn, C.: Untersuchungen über den Gallenfarbstoff beim Icterus neonatorum, Monatschr. f. Kinderh. **22**:1 (Oct.) 1921.
55. Rolleston, Humphey: Jaundice in the New-Born, Practitioner **109**:1, 1922; ibid, footnote 3.
56. Snapper, I.: Icterus, Ergebn. d. ges. Med. **4**, 1922.
57. Pollitzer, R.: Contributo statistico e ricerche sulla patogenesi dell'ittero dei neonati, Pediatria **32**:69, 1924.
58. Williamson, A. G.: Placental Iron and Its Relationship to Icterus Neonatorum, Surg. Gynec. & Obst. **37**:57, 1923.
59. Schiff, E., and Färber, E.: Beitrag zur Lehre des Icterus neonatorum, Jahrb. f. Kinderh. **97**:245 (March) 1922.
60. Decio, C.: Sul Contenuto in bilirubina del sangue gravidico e sull'ittero dei neonati, Ann. d. Fac. di med. e Chir. **27**:3, 1922.
61. Kraus, F.: Über Ikterus als führendes Symptom, Berl. Klin. Wchnschr. **58**:725, 1921.
62. Beyers, J. A.: Footnote 28.
63. Gessner, W.: Der Icterus Neonatorum und seine Beziehungen zur paraportalen resorption bei Beugeborenen, Gynäk. Rundschau **9**, 1915.
64. Luska: Casop. lék. Cesk. Abstr., Zentralbl. f. Kinderh. **14**:494, 1923.
65. Adler and Strausz, F.: Beitrag zum Mechanismus der Bilirubinreaction in Blutserum, Ztschr. f. d. ges. exper. Med. **44**:1, 1924.

in hemolytic icterus, as, for instance, the determination of the osmotic resistance of the red corpuscles. In using the sodium chlorid method, this resistance in cases of hemolytic icterus often is found to be lowered. In cases of icterus neonatorum definite changes have not yet been found (Gorter and Hannema,[66] Bodo Slingenberg,[67] Pollitzer,[68] Cserna and Liebmann [69] and others). Lately, Hornung [70] has examined the resistance by a more physiologic method, described by Brinkman,[71] whereby use is made of equilibrated salt solutions. By this method Hornung has found in icterus neonatorum an important raising of the osmotic resistance, which continues to rise during the first few days of life. According to Hornung, this result argues against icterus neonatorum being a hemolytic icterus, and at the same time it is an argument in favor of the supposition that in the pathogenesis of icterus neonatorum the main factor must be ascribed to the liver. As the experience acquired by this method in infants is not very large at present, we must await further confirmation.

In ascribing, on the ground of the results of the diazoreaction, the most important rôle to an excessive blood destruction as being the cause of icterus neonatorum, the investigators, before referred to, had in some degree returned to a former point of view. Formerly, it often had been supposed that icterus neonatorum was due exclusively or chiefly to an abnormally large blood destruction in the first days of life. This was supposed to be followed by a so-called pleiochromia and a polycholia, which meant a sudden formation of a large quantity of bile pigments. These could not be carried away directly through the bile capillaries and would in part enter the blood stream. In a closer study of this hemo-hepatogenic explanation, comparative determinations have been made of the number of red corpuscles and of the content of hemoglobin in icteric and in nonicteric children. Contrary to some investigators, who found an obvious decrease of the number of red blood corpuscles in icteric children, there were other workers who found no decrease. Recently, such determinations have been made by Lucas and his co-workers.[72] In 150 children, they systematically analyzed the

66. Gorter, E., and Hannema, L. S.: Ober de pathogenese van icterus neonatorum, Nederl. Maandschr. v. Verlosk. **2**:583, 1913.

67. Slingenberg, Bodo: Über Haemolyse in Beziehung zum Icterus neonatorum, Arch. f. Gynäk. **93**, 1910; ibid, Nederlandsch. Tijdschr. v. Geneesk., p. 1593, 1910.

68. Pollitzer, R.: Footnote 57.

69. Cserna and Liebmann: Footnote 30.

70. Hornung: Erythrozytenresistenz und Cholesteringehalt des Neugeborenblutes, Klin. Wchnschr. **4**:475 (March 5) 1925.

71. Brinkman, R.: Résistence osmotique et phosphatides du sang, Arch néerl. de Physiol. **6**:451, 1922.

72. Lucas, W. P.; Dearing, B. F.; Hoobler, H. R.; Cox, A.; Jones, M. R., and Smyth, F. S.: Blood Studies in the New-Born, Am. J. Dis. Child. **22**:525 (Dec.) 1921.

blood from the moment of birth for fourteen or more days. However, they did not find any difference between icteric and nonicteric children, either in the number of red corpuscles or in the content of hemoglobin.

In the meantime, of late there have appeared some new arguments for the idea that destruction of blood has much significance for the origin of icterus neonatorum. Looked on from a general point of view, the recent researches of Mann and Magath,[73] among others, demonstrating clearly the extrahepatic formation of bile pigments, may be regarded also as in favor of the hemolytic theory. Ylppö rejected the explanation of icterus neonatorum as due to an abnormally large destruction of blood. He based his rejection on the fact, established by him, that the total amount of bile pigments excreted in feces and urine during the first thirteen days of life, was not larger with icteric children than with those who were nonicteric. Further, he advanced the argument that there was no agreement between the degree of icterus and the total amount of excreted bile pigments. However important the fact of the constant excretion of bile pigments may be, and whatever explanation might be given for this fact, it need not stand in the way of an hematogenic explanation of icterus neonatorum, if one considers, that next to or perhaps even more important than the total amount of excreted bile pigments, is the total formation of bile pigments. Concerning this, Ylppö has said that the total formation is about the same with all new-born infants, but he did not prove this for the formation as he did for the excretion. In view of this, apparently quite rightly, P. H. Schwartz [74] recently declared that one is not justified in denying, *a priori,* that the increased destruction of blood is the most important factor in the causation of icterus neonatorum. After comparing the results of Ylppö and Hirsch with those of his own researches, he concluded that icterus neonatorum is caused by an increased destruction of blood, which takes place immediately after birth. With Baer and Weiser,[75] he has examined the iron metabolism of 114 new-born infants of different stages of development, in order to ascertain especially the effect of the manifold hemorrhages during birth. He found a typical curve for the change in the iron content in the liver and in the spleen of new-born infants. If the children were stillborn, whether full-term or premature,

73. Mann, F. C.; Bolliman, J. L., and Magath, T. B.: Bilirubin Formation After Total Removal of the Liver, Am. J. Physiol. **69**:393 (July) 1924. Mann, F. C., and Magath, T. B.: Die Wirkugen der totalen Leberextirpation, Ergbn. d. Physiol. **23**:212, 1924.

74. Schwartz, P.: Zur Frage des Icterus Neonatorum, Ztschr. f. Klin. Med. **100**:117, 1924.

75. Schwartz, P.; Baer, R., and Weiser, J.: Histologische Untersuchungen über den Eiweiszstoffwechsel im frühen Säuglingsalter, Ztschr. f. Kinderh. **37**:167, 1924.

or if they lived at most for three days, little or no iron was found in the liver or in the spleen. The older the children grew, the more iron was found, and this in a larger number of cells of liver and spleen. This increased until the first or second month, when iron was to be found in nearly all Kupffer's cells of liver and spleen. Just as Ylppö and Hirsch had found a typical curve for the change in the bile pigments of the blood after birth, so Schwartz and his co-workers have established this for the iron content. In both cases the curve was quite independent of the maturity of the fetus at the moment of birth. Therefore, Schwartz supposes that birth and the influence of birth cause a critical change in the metabolism of the bile pigments. He ascribes this to hemorrhages which occur in consequence of birth trauma, and he looks on icterus neonatorum as being a result of the destruction of this blood. Analogous views have been enunciated of late by Deluca [76] and to a certain degree also by Siegmund.[77] With premature infants, in whom the icterus is deeper than in those who are full grown, there would be association with the fact that traumatic hemorrhage at birth in premature infants generally is more severe. The same explanation may hold for children delivered by means of operation, in whom icterus neonatorum is also more frequent.[78].

Although proofs for the frequency of hemorrhage in new-born infants have been increased of late years through many and extensive researches, as, for instance, those of Sharpe,[79] Ylppö,[80] Ratnoff,[81] Warwick,[82] Ehrenfest,[83] Saenger,[84] Fischer,[85] Ulrich [86] and others, never-

76. Deluca, Francisco A.: Über den symptomatischen Icterus neonatorum, München med. Wchnschr. **69**:1254, 1922.

77. Siegmund, H.: Geburtschädijungen des kindlichen Gehirns und ihre Folgen, München. med. Wchnschr. **70**:137, 1923.

78. See footnote 1.

79. Sharpe, William: Intracranial Hemorrhage in the New-Born, J. A. M. A. **81**:620 (Aug. 25) 1923. Sharpe, W., and MacLaire, A. S.: Surg., Gynec. & Obst. **38**:200, 1924.

80. Ylppö, A.: Pathologisch-anatomische Studien bei Frühgeborenen, Ztschr. f. Kinderh. **20**:277, 1929.

81. Ratnoff, H. L.: Zur Frage von dem Wesen des Icterus neonatorum, Jahrb. f. Kinderh. **101**:187, 1923; ibid. Über das Vorkommen vonokkulem, Blut in den Faeces bei Säuglingen und im frühen Kindesalter, Ztschr. f. Kinderh. **34**:340, 1923.

82. Warwick, H.: Cerebral Hemorrhage of the New-Born, Am. J. M. Sc. **158**:96 (July) 1919.

83. Ehrenfest, H.: The Causation of Intracranial Hemorrhages in the New-Born, Am. J. Dis. Child. **26**:503 (Dec.) 1923.

84. Saenger, H.: Intrakranielle Blutengen bei Neugeborenen, Montaschr. f. Geburtsh u. Gynäk. **65**:258, 1924.

85. Fischer, B.: Der Einflusz des Geburtstraumata auf den Gehirn der Brustkinder, Schweiz. med. Wchnschr. **54**:905, 1924.

86. Ulrich, O.: Über Vorkommen und Prognose Geburtsträumatischer Blutungen im Cerebrospinalbereich, Ztschr. f. Kinderh. **39**:245 (March) 1925.

theless this theory of Schwartz lacks further experimental support, as he himself notes. Especially must the relation between the metabolism of bile pigments and of iron, in relation to the extent of the bleeding, be investigated. Some contradiction between the findings of Schwartz and those of earlier authors, such as Leuret,[87] who found the spleen in cases of icterus neonatorum already full of iron, might then be more closely examined. Moreover, the objection may be raised, which in this case has a special significance, namely, that manifest traumatic hemorrhages of new-born infants, such as cephalhematoma, are not always accompanied by deep icterus.

Of the before-mentioned writers, who found hemorrhages in newborn infants, Ratnoff especially must be mentioned. In a large percentage of cases of icterus neonatorum, this worker found occult blood in the feces (benzidin and guaiac test), whereas in nonicteric children he found it only in a small percentage of the specimens examined.

According to the growing significance which some workers attach to hemorrhage at birth as the causation of icterus neonatorum, the change in coagulation time must also be recalled. Of late years such a change—prolongation of the coagulation time—was noted by Fuhrmann and Bruno Kisch,[88] and by Greuter.[89] The last-mentioned investigator found this prolongation of the coagulation time in 72 per cent. of fifty-three infants, more especially in those with icterus neonatorum. This prolonged coagulation time reached its maximum at the third day of life and then slowly decreased to normal.

Lippmann,[90] in his extensive research on the histology of the blood of a large number of children during the first days of life, also examined the changes in the number of blood platelets; he did not notice any difference between icteric and nonicteric children. The same results were obtained previously by Emmanuele.[91].

An important argument for the rôle of the destruction of blood as a cause of icterus neonatorum has recently been presented by Haselhorst and Papendieck.[92] Against the explanation of icterus neonatorum being

87. Leuret, E.: Étude anatomo-pathologique comparée de l'icterè hémolytique du nouveau-né et de l'hémolyse provoquée. Nature hémolytique de l'ictère post-chloroformique, Arch. d. mal. du cœur, **3**:236, 1910.

88. Fuhrmann and Kisch, Bruno: Footnote 26.

89. Greuter, W.: Die Blutgerinnungszeit bei Icterus neonatorum, Ztschr. f. Kinderh. **35**:210, 1923.

90. Lippmann, H. S.: A Morphologic and Quantitative Study of the Blood Corpuscles in the New-Born Period, Am. J. Dis. Child. **27**:473 (May) 1924.

91. Emmanuele, A.: Richerche sulla piastrine e sulla coagulatilita del sangue nel neonato, Pediatria **31**:422, 1923.

92. Haselhorst, G., and Papendieck, A.: Hämatin als physiologischer Bestandteil des Blutes in der Fötalperiode und bei Neugeborenen, Klin. Wchnschr. **3**:979 (May 27) 1924.

caused by an increased destruction of blood outside the liver, it has for a long time been argued that the products of blood destruction are not present in the blood of new-born infants, as, for instance, hematin. Hellmuth [93] now and then did find hematin in the serum of the blood of the umbilical cord and often an oxyhemoglobinemia. Moreover, in 84 per cent. of 118 cases, Haselhorst and Papendieck found hematin in the serum. In twenty cases in which the blood was centrifuged and examined by the spectroscope immediately after withdrawal (in order to prevent a possible quick disappearance of the hematin line), they also found hematin in seventeen cases, or in 85 per cent. This hematinemia proved to be present in the first days of life nearly regularly and gradually disappeared in the course of the second week.

FIFTH GROUP

5. A separate place among the defenders of the theory of increased blood destruction as a cause of icterus neonatorum is taken by the Vienna pediatrician, Schick.[94] He says that this condition is a consequence of the destruction of the maternal blood, and more especially of the blood which is found in the intravillous spaces of the placenta. According to Schick, by this theory an explanation can be given for the different peculiarities of icterus neonatorum. Thus, the icterus of premature infants would be explained by the fact that the birth of these infants falls in a period of fetal life when an intensive transfer of destruction products of the blood of the mother takes place. This theory is based, among other theories, on the researches of Wagner,[95] who has found, as was found in earlier histochemical researches, that in the placenta of premature infants there is more iron present than in those of full term infants. Williamson [96] has found that a certain relation between icterus neonatorum and the iron content of the placenta exists.

The theory of Schick is also advocated by Schiff and Faerber.[97] These investigators found, however, contrary to Ylppö and Hirsch, and partly also contrary to other investigators, that the bilirubin content of the blood in cases of icterus neonatorum does not correspond to the appearance and the intensity of the icterus of the skin.[98] Therefore

93. Hellmuth, K.: Untersuchungen über Bilirubinaemie bei Neugeborenen zugleich ein Beitrag zur Genese des Icterus neonatorum, Monatschr. f. Geburtsh. u. Gynäk. **54**:341, 1921.

94. Schick: Footnote 8.

95. Wagner: Icterus neonatorum und Eisengehalt der Placenta, Ztschr. f. Kinderh. **27**:251, 1921.

96. Williamson: Footnote 68.

97. Schiff and Faerber: Footnote 59.

98. Hymans van den Bergh, A. A., and van Westrienen, L.: Feestb. voor H. Treub, p. 230, 1912. Hellmuth: Footnote 93. Lucas, C. S.: Footnote 72.

Schiff and Faerber suppose that there must be still another factor responsible for the appearance of icterus neonatorum, aside from the bilirubinemia caused by an increased destruction of blood. This is regarded by them as a disturbed permeability of the finer capillaries, caused by toxic or infectious toxic influences.[99] So far, this factor is insufficiently worked out. The workers did not make systematic bilirubin determinations; this has been done by Turolt and Tezner,[100] in order to judge the theory of Schick. These latter investigators have quantitatively determined the bilirubin content in the blood of the umbilical artery and of the umbilical vein separately. These researches, however, did not bring forth a positive result, for in some cases they found the larger content present in the artery; in others, the content in the vein was higher, quite independently of whether or not icterus was present. In this connection I must again refer to what I have said before in mentioning the researches of Cserna, which work, if it is confirmed, will be difficult to bring into agreement with the theory of Schick.

Schick has recently found another argument in favor of the view that in icterus neonatorum a principal rôle is played by factors which are already at work before birth. He[101] found, in fact, that the extension and distribution of the bile pigments in the skin in cases of icterus neonatorum take place according to the same laws as have been established for the measles exanthem by Pirquet.[102] The yellow color first appears on the highest parts of the back, then on the whole torso, the shoulders, the face and the extremities; later on, and then only in cases of severe icterus, do the fingers, toes and eyes also become yellow. The disappearance of the yellow tint takes place in the reverse order. In the same way as Pirquet did with measles, Schick tried to bring the extension of icterus neonatorum into relation with the vascular supply: the nearer to the heart, the larger is the deposit of bile pigments in the skin. With icterus neonatorum, Schick had not noticed a flaring up of the already decreasing icteric discoloration, contrary to what often has been established for icterus catarrhalis and other forms. According to Schick, this fact proves that only the bilirubin which is present at birth in the serum of the umbilical cord and which is formed during the first two or three days plays a rôle in icterus neonatorum; furthermore, that with icterus neonatorum only those factors which were already active before birth play a rôle.

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99. Ratnoff: Footnote 81.

100. Turolt, M. A., and Tezner, O.: Beitrag zur Genese des Icterus neonatorum, Zentralbl. f. Gynäk. **47**:1618, 1923.

101. Schick, B.: Über die Verteilung der Gelbfärbung in der Haut beim Icterus neonatorum, Ztschr. f. Kinderh. **38**:513, 1924.

102. Pirquet, C.: Das Bild der Masern auf der auszeren Haut, Berlin, J. Springer, 1913.

Against this theory, Ylppö [103] urged that only with difficulty can it be supposed that the material for the bilirubinemia comes from the blood of the mother, for icterus neonatorum often lasts for several weeks and with premature children even for months. According to him it is inconceivable that the products of the destroyed maternal blood should circulate for such a long time in the body of the child or that they could accumulate in some place or other and thus sustain the icterus. This at once raises the objection, first, that results such as those of Schwartz, mentioned before, concerning the changes in the iron deposit, certainly must speak in favor of the view that the destruction of the blood of children takes place slowly from the moment of their birth. Second, that those lasting forms of icterus of new-born infants may not always, as Ylppö supposes, be looked on as being cases of icterus neonatorum simplex.[104]. Schwartz also cannot accept the theory of Schick, because he fails to understand how it is possible that the histochemical iron curve begins always in the same way at the moment of birth, independently of whether the children are premature or full time. In general, the theory of Schick has found few adherents. Most of the investigators who wish to explain icterus neonatorum by an increased destruction of blood try to find a relationship with a destruction of blood taking place after birth.

COMMENT

At the end of this survey, though an enormous amount of work has been done, an explanation of the cause of icterus neonatorum, which is well grounded and sufficiently supported by experiments, is still far away. Aside from some irrefutable and important facts, there is still much contradiction between the results of the researches of different workers. Also it appears that there is no justification in assuming a connection between certain theories. In the first place it will be necessary to study more closely the significance of some new and important results. In conclusion, attention may be drawn, so far as these new results are concerned, to some further points.

Further results of histologic researches must be awaited to establish the theory of Quincke. So far as the theory of Ylppö is concerned, perhaps clearer proofs of the existence of the functional immaturity of the liver, both by means of the physicochemical analysis of the blood of new-born infants and by a study of the behavior of this blood with regard to the bile pigments will result. This should be of great significance, not only because this theory has many adherents, but also because many

103. Ylppö: Footnote 6.

104. Frank, F. S.: Aageboren haemolytische icterus by pasgeborenen, Nederlandsch Tijdschr. v. Geneesk. **67**:1849, 1923.

adherents of other theories are of the opinion that insufficient liver function also plays an important rôle. Next to this, researches on the permeability of the vascular wall of new-born infants may shed more light on the question. Further, it may be possible that an answer can more easily be given to the question as to why we find icterus at one time, and not at another, although the excretion of bile pigments is the same in both cases and there is but little difference in the degree of bilirubinemia. Finally, the difficult problems of the frequency, the significance and the extent of traumatic hemorrhage of new-born infants, in connection with the cause of icterus neonatorum have still to be solved.

Abstracts from Current Literature

Pathology, Bacteriology and Biochemistry

AN ESTIMATION OF THE CLINICAL VALUE OF THE VAN DEN BERGH TEST. ELIZABETH GLENN RAVDIN, Am. J. M. Sc. **169**:850, 1925.

Van den Bergh's test for the estimation of the quantity and type of bilirubin found in the blood and serum is discussed. Application of the test was made on the blood serum of 140 patients in whom there appeared to be indication for it, and comparisons were made of the direct and indirect readings obtained. In the cases of common duct stone and of occlusion of duct by tumor or pancreatic disease, there was a strong immediate direct reaction, with an indirect reading ranging from 1.4 to 18 units. The direct readings from nine patients with chronic cholecystitis were negative or delayed, the indirect reaction being normal in all but one case. Eleven cases of chronic calculus cholecystitis gave indirect readings from 0.2 to 1.9 units. In secondary anemia the indirect results were normal, in pernicious anemia between 0.6 and 4 units in all but one case studied. In hemolytic icterus anemia, results were high (from 1.5 to 4); in leukemia and purpura hemorrhagica the results were negative.

Van den Bergh's test and his interpretation of it as differentiating between the jaundice of obstruction and hemolysis, is in accord with these clinical findings.

PARSONS, Ann Arbor, Mich.

OBSERVATIONS ON BLOOD LACTIC ACID AFTER INSULIN. CHARLES H. BEST and J. H. RIDOUT, J. Biol. Chem. **63**:197, 1925.

The authors made simultaneous observations on the quantity of glucose and lactic acid in the blood of normal and diabetic dogs before and following the injection of insulin. The decrease in the blood sugar was much more than would be accounted for by a small increase in the lactic acid. Thus, the decrease in the blood sugar following injection of insulin does not seem to be explained by a change into lactic acid. Hypoglycemic convulsions, however, will increase the lactic acid of the blood.

NOTE ON THE CONCENTRATION OF THE ACETONE BODIES IN NORMAL BLOOD AND URINE. ROGER S. HUBBARD and CHARLES V. NOBACK, J. Biol. Chem. **63**: 391, 1925.

The authors have gathered data from twenty-nine tests as to the quantity of acetone bodies in the samples of blood and urine obtained simultaneously. They conclude that the percentage of acetone bodies in the blood and urine in a large majority of cases agreed within the limits of accuracy of the method of determination.

THE EXTRACTION OF A PARATHYROID HORMONE WHICH WILL PREVENT OR CONTROL PARATHYROID TETANY AND WHICH REGULATES THE LEVEL OF BLOOD CALCIUM. J. B. COLLIP, J. Biol. Chem. **63**:395, 1925.

The author has extracted an active principle from the parathyroid glands of oxen, which will prevent the symptoms of tetany in parathyroidectomized

dogs. The extract is prepared by digesting the glands for one hour with 5 per cent. hydrochloric acid at 100 C.; the digest is made alkaline and then freed of protein; the resulting aqueous solution can be used either by mouth, intravenously or subcutaneously. This active principle in preventing the tetany raises the calcium content of the blood.

When an overdose of the principle was used, a symptom complex is obtained, which is called hypercalcemia by reason of the high calcium content of the blood (from 15 to 18 mg. per hundred cubic centimeters blood serum, normal, from 10 to 11 mg.). The symptoms of hypercalcemia were loss of appetite, dulness, drowsiness, coma, general atonia. There was obvious dehydration, as seen from the concentration of the blood; when the animals were in the condition of hypercalcemia, it was difficult to withdraw blood from the veins and also to separate the serum from the specimen obtained.

Hypercalcemia can be overcome by administration of sodium bicarbonate. If allowed to persist, hypercalcemia will result fatally.

Parathyroidectomized dogs will not develop tetany if they receive this extract once or twice daily; if the administration of the extract is discontinued, tetany ensues.

This hormone, affording a means of increasing the calcium of the blood, will doubtless prove of value in many medical conditions, when the calcium metabolism is disturbed. The hormone therapeutically will be dangerous, if unscientifically used, owing to the bad effects of overdosage. Its ultimate merits or demerits will be determined only by careful clinical studies.

Clinical Calorimetry. XXXVIII. The Utilization of Carbohydrate in a Case of Renal Glycosuria. William S. Ladd and Henry B. Richardson, J. Biol. Chem. **63**:681 (April) 1925.

A boy, Jewish, aged 12 years, had persistent glycosuria with no symptoms of diabetes mellitus, and a normal blood sugar. The diagnosis of renal diabetes was made. The boy was studied in the respiration calorimeter; the respiratory quotient rose from .816 to .926 following the ingestion of 150 gm. of glucose, 36 gm. appearing in the urine in twenty-four hours. The ability to oxidize carbohydrate was not impaired in this patient; renal diabetes does not appear to be a preliminary stage of diabetes mellitus.

A Method of Obtaining Blood from Veins, Similar to Arterial Blood in Gaseous Content. Samuel Goldschmidt and Arthur B. Light, J. Biol. Chem. **64**:53, 1925.

The authors found that blood, taken from superficial veins on the back of the hand after the hand had been immersed in hot water (45 C.), had the same percentage of oxygen saturation and carbon dioxid content as arterial blood.

The Effect of Ultraviolet Irradiation on the State of the Serum Calcium. Alan R. Moritz, J. Biol. Chem. **64**:81, 1925.

Rabbit's whole blood and blood serum and human blood serum in quartz tubes were irradiated by ultraviolet light. The calcium of the serum was unchanged; the diffusible calcium (that is, not combined with the protein of the serum) was also unchanged. The hair of rabbits was shaved off; the

rabbits were then exposed over a period of three hours to ultraviolet light; no change was found either in the total or the diffusible calcium of the rabbit's serum after the irradiation. One animal was irradiated intermittently over a period of six days without any change in the calcium of the serum. Approximately from 45 to 60 per cent. of the calcium of rabbit's blood seurm is diffusible.

A Simple Method for Obtaining Cutaneous (Capillary) Blood from Infants and Adults for Colorimetric p_H Determination. Paul Drucker and Glenn E. Cullen, J. Biol. Chem. **64**:221, 1925.

It is necessary for the accurate determination of the carbon dioxid content or the hydrogen ion concentration of blood, that the blood is not exposed to the air. The authors offer a method for obtaining capillary blood from an infant's heel for such determinations.

The foot is put in hot water to produce a hyperemia and then dried. The heel is then placed in a glass funnel, the bottom of which is closed; the funnel contains paraffin oil.

An incision with a cataract knife is made under the oil and the blood thus collected without exposure to air.

Higgins, Cincinnati.

Jaundice as an Expression of the Physiological Wastage of Corpuscles. Peyton Rous and D. R. Drury, J. Exper. Med. **41**:601, 1925.

Biliary obstruction was produced in a series of dogs by cutting the common duct between ligatures. The cystic duct was also severed to rule out the influence of the gallbladder to delay jaundice. The hemoglobin percentage and bilirubin content of the blood, and the bilirubin excretion in the urine were followed from day to day. Routine examinations of the urine made for evidence of kidney injury showed at the most only the slightest disturbance that is not uncommon in the first weeks of jaundice.

In two charts of typical findings in individual dogs the authors point out that, after an initial period when the chloroform anesthesia provided a cause of complication, the changes in bilirubinemia correspond notably in time and degree with similar variations in the hemoglobin percentage of the blood. The course of events found irregular expression in the output of bilirubin through the urine. Removal of a portion of the circulating blood pigment by bleeding resulted in a corresponding, or more than corresponding, reduction in bilirubinemia. With recovery from the anemia the bilirubinemia curve mounted with that of the hemoglobin.

The close correspondence in the changes in bilirubinemia with the changes in circulating hemoglobin, even when the tissue icterus is of long standing, indicates, in the opinion of the authors, the presence of a barrier (the walls of the blood vessels) to the distribution of bile pigment from the blood. The influence of the barrier is evidenced by the relatively negligible amount of bile pigment in the lymph compared with that in the blood in the long jaundiced animal.

The authors further conclude that the jaundice that develops after obstruction of the common duct in the absence of complications, expresses the physiologic wastage of corpuscles occurring from day to day; and the intensity of the bilirubinemia varies as does the total of functioning hemoglobin —containing tissue from which this wastage takes place.

McClure, Evanston, Ill.

SIGNIFICANCE OF THE MASTIC REACTION IN PEDIATRICS. SIEGFRIED LEVY, Monatschr. f. Kinderh. **30**:33, 1925.

The writer used a modification suggested by Goebel in which only six tubes are necessary. He also reports on eighty cases. His series is noteworthy, as he believes the test aided the diagnosis of epidemic encephalitis, although this may readily be confused with tuberculous meningitis.

GERSTLEY, Chicago.

STUDIES ON ELIMINATION OF ACIDS IN THE URINE OF CHILDREN. PART 1. ON THE ACIDITY OF URINE AND ITS DETERMINATION. J. BROCK, Ztschr. f. klin. Med. **101**:51, 1925.

It is shown by the author that the determination of primary and secondary phosphates in the urine through titration with alkali and phenolsulphonephthalein or with acid and methyl orange is theoretically impossible and practically false. The same thing is true of the estimation of actual reaction and of "acid elimination" in the urine based on these methods.

For the direct determination of acid elimination or more correctly of the surplus of acid in the urine, the author describes his own titration method, which is very simple and should take the place of the usual "titration acidity."

For a scientific analysis of the acids of the urine — besides the colorimetric determination of its actual reaction and of the ammonia coefficient — it is necessary to differentiate between inorganic and organic weak acids as factors of acidity. While for the former ones we have an old and reliable method in the phosphate titration with uranyl acetate, the author recommends for the latter ones a new method of Van Slyke and Palmer.

In connection with this, a new simple method is described for the determination of the strength of these organic acids as it is expressed in the dissociation constant.

ZENTAY, St. Louis.

Nutrition

THE RELATIVE VALUE OF ULTRAVIOLET LIGHT AND IRRADIATED AIR IN PREVENTING RICKETS IN CHICKENS. J. S. HUGHES, CHARLES NITCHER and R. W. TITUS, J. Biol. Chem. **63**:205, 1925.

Experiments were made on three groups of chickens. Group 1 served as a control. Group 2 were irradiated for ten minutes twice a day with ultraviolet light from a quartz mercury vapor lamp. Group 3 were given a treatment of irradiated air for ten minutes twice a day. All the chickens in Group 1 and 3 developed rickets, while those in Group 2 did not develop rickets.

Analysis of the dried bones for calcium and phosphorus showed the following results:

	Calcium, Per Cent.	Phosphorus, Per Cent.
Group 1	5.75	2.86
Group 2	6.85	3.36
Group 3	5.75	2.96

A FURTHER REPORT ON IMPARTING ANTIRACHITIC PROPERTIES TO INERT SUBSTANCES BY ULTRAVIOLET IRRADIATION. ALFRED F. HESS and MILDRED WEINSTOCK, J. Biol. Chem. **63**:297, 1925.

This article includes observations on the effect of irradiation of various food substances on the protection of rats from rickets. Linseed oil retained its nonrachitic properties six months after irradiation. Lettuce leaves irradiated

three days previously and green wheat two weeks previously still contained antirachitic properties, while the nonirradiated substances did not protect against rickets. The chlorophyl content of vegetables had no bearing on their antirachitic properties; a solution of chlorophyl when irradiated was not antirachitic. Neither blood cells, blood serum, cream, phosphatid extracted from egg yolk nor glycerine were given antirachitic properties by irradiation.

The antirachitic property of cod liver oil is in the nonsaponifiable portion. Unless the nonsaponifiable portion of linseed oil has been irradiated, it does nor glycerin were given antirachitic properties by irradiation.

THE ANTIRACHITIC VALUE OF IRRADIATED PHYTOSTEROL AND CHOLESTEROL. I. ALFRED F. HESS, MILDRED WEINSTOCK and F. DOROTHY HELMAN, J. Biol. Chem. **63**:305, 1925.

Phytosterol, which is a main constituent of the nonsaponifiable fraction of vegetable oils, was prepared from cottonseed oil. This product protected rats against rickets only when it had been irradiated. Cholesterol was prepared from brain tissue and showed the same antirachitic properties as phytosterol.

The authors suggest the following hypothesis to explain the protection from rickets by sunlight. The epidermis of the skin contains cholesterol; solar rays and artificial irradiation render the cholesterol antirachitic; this activated cholesterol is transported by the circulation throughout the body.

THE RESISTANCE OF THE ANTIRACHITIC SUBSTANCE IN COD LIVER OIL TO REAGENTS. CHARLES E. BILLS, J. Biol. Chem. **64**:1, 1925.

Cod liver oil was subjected to various reagents to ascertain if the antirachitic vitamin was destroyed. Tests for the vitamin were made by feeding the oil incorporated in a rickets producing diet. Hydrogen peroxid, hydrogen sulphid, sulphur dioxid, and formaldehyd did not destroy the vitamin. Nitrous fumes made from the action of acetic acid on sodium nitrite rapidly destroyed the vitamin. Direct steam slowly destroyed the vitamin. Acid hydrolysis of the oil also slowly destroyed vitamin.

THE ANTISCORBUTIC PROPERTIES OF EGGS. SIGFRED M. HAUGE and CAREY W. CARRICK, J. Biol. Chem. **64**:111, 1925.

Eggs did not cure guinea-pigs with scurvy, nor prevent nor delay the onset of scurvy in animals on a scurvy-producing diet. The chicks growing in the shell may synthetize any needed vitamin C.

THE ANTIRACHITIC VALUE OF IRRADIATED CHOLESTEROL AND PHYTOSTEROL. II. FURTHER EVIDENCE OF CHANGE IN BIOLOGICAL ACTIVITY. ALFRED F. HESS and MILDRED WEINSTOCK, J. Biol. Chem. **64**:181, 1925.

The capacity of a food to become antirachitic following ultraviolet irradiation seems to depend largely on the presence of phytosterol or cholesterol. Dried milk will not prevent rickets unless irradiated. Spinach also does not prevent rickets unless irradiated, but after irradiation will retain its antirachitic property even after it has been boiled for thirty minutes.

Cholesterol was irradiated and injected subcutaneously into rats on a rickets producing diet; the rats did not develop rickets. Cholesterol and phytosterol lose the power of preventing rickets after irradiation, when they have been reduced to dihydrocholesterol and dihydrophytosterol — the double

bond being eliminated from the molecule. Cymene and citronella oil, although chemically somewhat similar to phytosterol, did not acquire antirachitic properties after irradiation.

In a previous paper, the authors presented the theory that cholesterol in the skin was the agent through which heliotherapy or light therapy prevented and cured rickets. Rats on an antirachitic diet were fed irradiated skin and did not develop rickets, while control animals fed nonirradiated skin became rachitic.

Experiments with light filters in irradiating cholesterol solutions seem to show that rays of 302 microns wave length or less are necessary to confer antirachitic property.

THE ANTIRACHITIC VALUE OF IRRADIATED CHOLESTEROL AND PHYTOSTEROL. III. EVIDENCE OF CHEMICAL CHANGE AS SHOWN BY ABSORPTION SPECTRA. ALFRED F. HESS and MILDRED WEINSTOCK, J. Biol. Chem. **64**:193, 1925.

Cholesterol which had been irradiated by ultraviolet light was found to have changed in its ability to absorb ultraviolet radiations; this seems to indicate a chemical change in the cholesterol. This change ordinarily disappears within a relatively short period unless the cholesterol is kept in an oily medium.

HIGGINS, Cincinnati.

FACTORS INVOLVED IN THE ACIDITY OF THE STOOLS OF INFANTS. ALLAN BROWN and FREDERICK F. TISDALL, N. Y. State J. Med. **25**:152, 1925.

From over 1,300 determinations of the p_H of infants' stools, the variation in acidity for those of breast fed infants was found to be between p_H 4.7 and 5.1; and for those of artificially fed infants from p_H 4.6 to 8.3 or somewhat more alkaline. Acidity as great as p_H 4.6 was found only in artificially fed infants with severe diarrhea. Infants fed on butter soup had stools with an acidity of about p_H 6.0. Under protein milk, cow's milk with added carbohydrates, and whole soured milk with added carbohydrates the stools were generally more alkaline than p_H 7.0. When the carbohydrates added to the whole soured milk reached 20 per cent., the stools were strongly alkaline. The effect from the addition, whether in the form of corn syrup, dextrimaltose or cane sugar was the same.

Parenteral infections were generally accompanied by increased acidity of the stools.

"The acidity apparently depends on the ratio in the intestinal zone of fermentation, of the carbohydrate on the one hand to the protein and base on the other. The amount of carbohydrate in the zone of fermentation, apparently is influenced by the extent of the zone of fermentation, by the type of carbohydrate and by the state of health of the intestinal cells."

The method of Tisdall, described in AMERICAN JOURNAL OF DISEASES OF CHILDREN, April, 1924, was employed in the study.

GRAVES, New York.

EXTREME SENSITIZATION IN INFANTS TO COW'S MILK PROTEIN. FREDERICK F. TISDALL, Canad. M. A. J. **15**:497, 1925.

The authors review briefly the theories of sensitization to protein and the general symptomatology. Two cases are reported in detail.

In both cases the family history showed some member of the family with protein sensitization. The symptoms in both cases were similar — refusal of milk after the first few swallows, evident pain, irritability, swelling of lips, vasomotor changes in skin and shock. Rapid breathing and cyanosis were present in one case. The treatment consisted of increasing doses of milk beginning with 1 drop.

MOORE, Omaha.

FURTHER OBSERVATIONS ON NUTRITION WITH DIETS RICH IN PROTEIN. V. B. READER and J. C. DRUMMOND, J. Physiol. **59**:472-478, 1925.

Rats failed to grow to adult size when fed on diets containing a high proportion of protein (from 45 to 90 per cent.). The animals appeared to be in good health and the consumption of food was satisfactory. Postmortem examination revealed no abnormality other than hypertrophy of the kidneys, as measured by the ratio of kidney to body weight. The slight degeneration changes observed in some of the kidneys of rats fed on diets high in protein could not be ascribed to the action of the food, as similar changes were seen in the controls. Excretion of relatively large amounts of nitrogen (2.5 gm. daily) over periods of four months does not appear to damage the kidneys of rats.

KUGELMASS, New Haven, Conn.

OBSERVATIONS ON VITAMIN CONTENT OF MILK. L. F. MEYER and E. NASSAU, Monatschr. f. Kinderh. **29**:505, 1925.

Experimental observations on the market milk obtained in Berlin showed that it did not contain antiscorbutic properties. Pasteurization, oxidation by a stream of air and the addition of hydrogen peroxid destroy this property. Preserving by the addition of soda is not effective.

CONTRIBUTION TO ALIMENTARY INTOXICATION. F. THOENES, Monatschr. f Kinderh. **29**:717, 1925.

As the clinical picture of alimentary intoxication (Finkelstein) is associated with extreme water loss and with symptoms of grave disturbance of the central nervous system, the author attempted to demonstrate by chemical analyses some changes in the mineral and water content of children dying of this condition. His results confirm those of other observers. His analyses were those of the brain of children who had died less than twelve hours previously. There was little difference between the analyses of the original cases and the controls. With our present methods, at least a diminution of the water and the mineral content could not be demonstrated.

The writer suggests the view already advocated by others that the changes in water metabolism in this condition are not purely quantitative but are changes in the method by which water is held in the tissues.

GERSTLEY, Chicago.

COMPARISON BETWEEN THE MEDICINAL-DIETETIC AND THE LIGHT TREATMENT OF RICKETS. I. JUNDELL, Acta Pediat. **4**:204 (April) 1925.

A detailed report of thirty-four patients with rickets, some of whom were treated with ultraviolet radiation, while others were treated on a low diet with addition of cod liver oil, phosphorus and tricalcium phosphate. In both

series of cases the healing was equally satisfactory. The author believes there are special indications for these two forms of treatment. The medicinal-dietetic treatment is to be preferred: (*a*) when the child is overfed, and (*b*) when light therapy is impracticable. Ultraviolet radiation is preferable when for any reason a high caloric diet is indicated or there is any reason to think that the child would not tolerate a low diet for a suitable length of time.

HOLT, Baltimore.

LIGHT AND THE ANTIRACHITIC FACTOR. C. E. BLOCH and FRANS FABER, Ugesk. f. Laeger., 1925, p. 392.

A definite increase of the phosphorus content in the blood of rachitic children after treatment with the mercury quartz lamp was demonstrated. The diet of these children was either left as it was before they became sick, or milk and carbohydrates were substituted.

Children with uncomplicated tetany on similar diets showed a marked increase in the calcium content of blood after exposure to the mercury quartz lamp. It was necessary to give these children from 0.25 to 0.5 gm. of chloral shortly before irradiation in order to prevent spastic or eclamptic attacks.

The authors think that irradiation of the body may effect a general activating influence on any hypofunction. In order to prove this contention, blood sugar values are shown before and after irradiation of a fasting diabetic patient. These figures are, however, not conclusive.

It is inferred in the conclusion that probably no antirachitic vitamin exists, for irradiation of various food substances will cure experimental rachitis just as irradiatin by the mercury quartz lamp will cure rachitis in infants. These observations make it appear that ultraviolet light is an activating and regulating force on body metabolism and that the mode of action, based on recent research work, may be brought about by changes in the chemical structure of organic substance through irradiation.

SCHLUTZ, Minneapolis.

Prenatal Conditions

DORSAL SLITTING OF THE INTESTINE IN RACHISCHISIS. H. LEHMANN-FACIUS, Frankfurt. Ztschr. f. Path. **31**:479, 1925.

Abnormality of the intestine associated with cleavage of the vertebrae may be divided into three groups: wide ectopias, fission of the intestine and abnormal point of exit of the intestinal tract. He describes a 7 month's fetus with total craniorachischisis and the typical appearance and posture of an anencephalic monster. There is a wide dorsal cleft, into which two fistulas open, the upper is just beneath the base of the skull and represents the lower end of the foregut; the lower fistula leads from the caudal end of the cleft into the hind gut, which opens through the anus after a short course. Between the two openings into the dorsal cleft is a sac-like tumor which contains the stomach, intestines, pancreas and spleen. There were also a double uterus and paired vaginae. The author explains the dorsal anomaly by stating that the entoderm has failed to close over in the midline behind, between the esophagus and the rectum. He discusses various theories to account for this.

FOOT, Cincinnati.

Diseases of the New-Born

ASPHYXIA IN A NEW-BORN INFANT FROM FAULTY DEVELOPMENT OF THE TONGUE FRENUM. W. COURTIN, Monatschr. f. Kinderh. **30**:60, 1925.

The writer gives a history of a new-born child who suffered from repeated attacks of asphyxia. The etiology was finally traced to an imperfectly developed frenum of the tongue. The child gradually outgrew the difficulty.

GERSTLEY, Chicago.

ESOPHAGO-LARYNGO-TRACHEAL FISTULA. L. MEILI, Frankfurt. Ztschr. f. Path. **31**:525, 1925.

This is a report of an infant, aged 5 days, in whom the entire posterior laryngeal wall was cleft, communicating with the pharynx and esophagus; the cleft extended 1 cm. or so into the posterior tracheal wall also. Meili explains this as being a failure of union on the part of the lateral ridges or folds, of the foregut. He reviews the literature on this form of anomaly.

FOOT, Cincinnati.

Acute Infections

STUDIES ON THE ETIOLOGY OF ACUTE RHEUMATIC FEVER. B. J. CLAWSON, J. Infect. Dis. **36**:444, 1925.

Organisms were isolated from twenty cases of well defined, acute rheumatic fever, rheumatic endocarditis or chorea. The organisms were obtained by blood culture and injected, in large doses, into animals three times a week.

The organisms were streptococci, usually arranged as diplococci and were found to be nonproducers of green discoloration on blood agar plates. They were said to be in the fecalis group. It was demonstrated that agglutination does not differentiate strains of rheumatic origin from strains of subacute bacterial origin.

On the basis of morphologic, cultural and immunology characteristics, Clawson feels that the group cannot be considered a specific one, but that it represents a heterogeneous group, generally green producers with moderately low virulence.

The results of his animal experimentation, with 12 strains isolated in cases of acute rheumatic fever and 1 strain isolated in a case of subacute bacterial endocarditis, agree with what many investigators have shown, namely, that lesions grossly similar to human rheumatic endocarditis can be produced in rabbits by injecting streptococci.

Myocarditis was present in all cases in which endocarditis occurred, except three. The lesions contained large mononuclear and multinucleated cells with vesicular nuclei. Some of the nodular lesions were similar morphologically and in all respects with the Aschoff nodules in human cases of rheumatic carditis.

He concludes that:

1. In a relatively high percentage of cases of acute rheumatic fever, a streptococcus can be isolated from the blood.

2. This streptococcus generally belongs to the viridans group. It does not seem to be a specific strain.

3. Lesions similar to those occurring in human rheumatic fever can be produced experimentally by injecting these organisms.

4. When these facts are considered, there seems to be ground for the belief that rheumatic fever with its associated lesions is produced by streptococci.

5. A positive blood culture in liquid medium should not form a positive basis for a diagnosis of subacute bacterial endocarditis.

6. There is a strong suggestion that rheumatic endocarditis and subacute bacterial endocarditis may be produced by the same agent, and are but different degrees of the same process.

KENNEDY, Rochester, Minn.

THE TREATMENT OF PERTUSSIS BY THE METHOD OF AUDRAIN. RAMÓN GIMÉNEZ GUINEA, Arch. españ. de pediat. **8**:605, 1924.

This method consists in the intramuscular injection of sulphuric ether at a temperature of 66 C. The injection is given in the buttocks and generally on alternate days. In infants under 6 months, 1 c.c. is given. In those over 6 months, 2 c.c. is used. To the older infant and child up to adolescence, from 3 to 5 c.c. can be given.

By this method the paroxysms of the cough can be rapidly controlled and decidedly shortened. The vomiting diminishes or ceases after the first or second injection.

The author has never observed untoward general or local reactions.

For a complete cure, eight or nine injections may be required. In severe cases complicated with bronchopneumonia, daily injections may be given instead of on alternate days.

SCHLUTZ, Minneapolis.

PNEUMONIC ICTERUS IN INFANCY. OSCAR ROSONI, Clin. Pediat. **7**:223-240, 1925.

As compared to the frequency in adults, icterus as a complication of pneumonia in infancy is comparatively rare.

The author believes that the icterus in this disease is not of a catarrhal type; nor is it due to some gross liver pathology involving structural changes in the hepatic parenchyma; but that it is due to some pathogenic influence of the pneumococcus on the blood constituents. This is presumably of the nature of a hemolysis.

The icterus in these cases generally disappears with the subsidence of the pneumonic process.

Four cases occurring in infants are reported.

DIPHTHERIA IN THE NEW-BORN. ETTORE PARIGI, Clin. Pediat. **7**:242-249, 1925.

Four cases of diphtheritic rhinitis in the new-born are reported.

In one case the disease appeared during the first week of life; in the second case after the first month; in the third and fourth cases (twins) during the first few days.

In the presence of a mild rhinitis in the new-born, it is well to think of diphtheria. The diagnosis may be confirmed by laboratory examination of the secretion. This is to be investigated especially in those cases that are refractory to ordinary treatment. Serum therapy, properly instituted, gives prompt recovery.

In none of the reported cases was pharyngeal involvement noted. Antidiphtheritic serum was used in treatment.

ZAMBARANO, Washington, D. C.

HELMINTHIASIS IN INFANCY. HERMANN BRÜNING, Monatschr. f. Kinderh. **29**:736, 1925.

This is a review of the literature of 1923 on the subject of intestinal parasites in children. There is nothing new in the article.

Eosinophilia was found frequently though not invariably. In some cases this did not develop until treatment had been taken to get rid of the worms. The clinical symptoms are not definite, and no special method of determining the ova in the stools is recommended. A few reports of unusual surgical complications are of interest. The condition is not infrequently confused with appendicitis. Occasionally symptoms of intestinal obstruction are simulated. In rare cases laparotomy revealed worms free in the abdominal cavity.

There is also a summary of all the different treatments recommended, but with no particular recommendation by the writer.

CIRCULATORY DISTURBANCES FOLLOWING MEASLES. W. HANDEL, Monatschr. f. Kinderh. **30**:55, 1925.

The writer gives histories of two cases of measles, complicated by circulatory disturbances of the extremities.

Case 1 was a child, aged 10 months. On the sixth day following the appearance of the rash, an edematous swelling developed on the arms and legs below the elbow and knee joints. The color was blue-red and was sharply differentiated from the healthy skin. Repeated applications of hot dressings and massage continued for several days and nights resulted in cure.

Case 2 was a child, aged 21 months, with measles complicated by pneumonia. On the eighth day and two days before death, a waxy pallor and coldness appeared in the right foot. It then spread to the knee. The next day the left foot became involved. The disturbance progressed gradually upward to the umbilicus when death occurred on the same day.

The writer assumes in each case that there was a toxic injury to the capillaries.

GERSTLEY, Chicago.

BACTEREMIA CAUSED BY DIPHTHERIA BACILLI. ROOSEN RUNGE, Virchows Arch. f. path. Anat. **254**:379, 1925.

The literature indicates that in deaths from diphtheria, the occurrence of diphtheria bacilli in various body organs is not associated with specific organ changes. Even in instances when diphtheria bacilli have apparently been found in the blood stream at necropsy, it has been shown that avirulent forms predominate. Bernard and Paneth lent support to this view by demonstrating that diphtheria bacilli lost their virulence on injection into the blood streams of dogs and guinea-pigs. Runge reports the interesting protocol of a child, aged 2½ years, in whom diphtheritic bacteremia was demonstrated. The child became ill with an upper respiratory infection, followed by swelling of the feet, generalized edema, ascites, numerous petechial hemorrhages of the skin and a temperature ranging from 38 to 39 C. (from 100 to 102 F.). A systolic murmur was audible over the entire heart. The blood picture was of anemia with leukocytosis. Death occurred in three days. Blood culture at entrance and death showed diphtheria bacilli. Section showed septic endocarditis of tricuspid valve, hydrothorax, hydropericardium and hemorrhagic infarcts in

right lower lobe. Runge attempts to explain the profuse growth of bacteria in the blood stream on the basis of the work of Lorentz, who was able to vary the activity of growing diphtheria bacilli in vitro by changing the acidity of the culture mediums. In this instance, the lesion on the venous side of the heart brought about such change in vivo.

SCHWARZ, Milwaukee.

Chronic Infections

THE WASSERMANN TEST. XIV. THE EFFECT OF SULPHARSPHENAMIN ON THE WASSERMANN REACTION. DAVID L. BELDING, Arch. Dermat. & Syph. **11:** 736 (June) 1925.

The quantitative effect of intensive sulpharsphenamin treatment on the Wassermann reaction was observed in late hereditary syphilis in childhood and in acquired syphilis in various stages in adults. No advantage was found in sulpharsphenamin over arsphenamin. Sulpharsphenamin did not alter the treatment fast condition occurring during arsphenamin treatment. The intensity of the treatment is a greater factor in reducing the Wassermann reaction than the total dosage. Clinical effects were fully as good as with arsphenamin. No noteworthy difference in the clinical results was observed between those patients treated intramuscularly and those treated intravenously. Children are able to tolerate proportionately larger doses of sulpharsphenamin than adults.

THE VALUE OF FLUMERIN IN THE TREATMENT OF SYPHILIS. JAMES C. FOX, GEORGE H. GILDERSLEEVE and JOHN F. PRESTON, Arch. Dermat. & Syph. **11:**768 (June) 1925.

Flumerin is the result of an attempt to find an organic mercury salt of therapeutic value, with low toxicity, and without irritant properties. It is given intravenously. It is found to be inferior to the arsphenamins, but superior to the other mercurials in common use. The optimum dose is 4 mg. per kilogram of body weight, twice a week, until from 8 to 12 injections have been given. Reactions severe enough to cause interruption of treatment occurred in 21 per cent. of the cases.

JEANS, Iowa City.

CONGENITAL SYPHILIS. C. NELKEN, Med. Klin. **20:**1462, 1924.

Sixty-five cases of congenital syphilis were studied. Few of these patients showed evidences of syphilis at birth, but in half of them the family history gave a strong suspicion. Thirteen infants were premature. In forty cases the signs of congenital syphilis became manifest in the first four months of life. Less than half of the patients came to the Clinic with a diagnosis of syphilis. In four cases with cardinal signs of the disease, the Wassermann reaction was negative. The mortality was almost 50 per cent. The epitrochlear enlargement was not constant; this is not of great value since it is often found in older children with no evidence of syphilis. Nelken has seen rhagades in a definitely nonsyphilitic child. Of the forty children whose skeletal systems were roentgenographed, twenty-seven showed bone lesions. A description is given of the treatment. The negative Wassermann reaction was no indication of a cure.

PETERMAN, Rochester, Minn.

CLINICAL USEFULNESS OF THE NEW SERODIAGNOSTIC METHODS IN TUBERCULOSIS. F. KLEMPERER and A. SALOMON, Ztschr. f. klin. Med. **101**:1, 1925.

The complement fixation tests with the antigens of Wassermann and Besredka give only positive results in a majority of undoubtedly tuberculous cases (73.2 and 89.5 per cent. respectively).

The reactions give a positive result in a considerable number of cases without any signs of an active process of tuberculosis (27 and 46.7 per cent. respectively).

They therefore are of no value in dubious cases in which their practical importance would be the greatest.

ZENTAY, St. Louis.

ALLERGY, PRIMARY LESIONS AND MILIARY TUBERCULOSIS. R. KORTEWEG and E. LOEFFLER, Frankfurt. Ztschr. f. Path. **31**:136, 1925.

This is an interesting experimental investigation, in which the writers have endeavored to establish the relationship of miliary tuberculosis to allergy. They first experimented on ten subcutaneously inoculated animals to determine whether the kidney and bone marrow (which are commonly supposed to escape infection under these conditions in guinea-pigs) would show tubercles. In four out of ten guinea-pigs, lesions were produced in the kidney, showing that a hematogenous infection may follow subcutaneous inoculation. They then carried out two series of experiments in animals previously inoculated subcutaneously or intradermally. In one set they injected eleven million tubercle bacilli into the left side of the heart, which was approached through the left lung. These bacilli were in the finest possible suspension. A bacillemia resulted, with an occasional slight lesion, but no general miliary tuberculosis. In the second series they injected from 0.2 to 0.5 c.c. of a suspension in which the bacilli were in coarse, visible clumps and masses. Here they produced typical miliary tuberculosis.

They conclude that the kidney and bone marrow may become hematogenously infected following subcutaneous inoculation in guinea-pigs. One can produce a miliary tuberculosis only under conditions of allergy, otherwise "primary lesions" ("Primäraffekte") and not miliary tubercles result. Injections of tubercle bacilli in fine suspension into the blood of guinea-pigs produces bacillemia, without miliary tuberculosis. Miliary tuberculosis results only after the intravenous injection of coarse, visible suspensions of tubercle bacilli. There is a strong tendency to healing in the experimental miliary tuberculosis of guinea-pigs. The histologic picture and development of the primary lesion and the miliary tubercle differ throughout their entire course. Writers frequently speak of "miliary tubercles" when they mean "primary lesions."

FOOT, Cincinnati.

THE INFLUENCE OF SUNLIGHT AND QUARTZ LIGHT ON THE BLOOD PICTURE OF TUBERCULOUS CHILDREN. I. KOPITS, Orvosi hetil. **69**:124, 1925.

Under the influence of exposure to sunlight or to ultraviolet light, the following changes were observed in the blood picture of tuberculous children:

The hemoglobin content increases, the color index shows varied changes, the red blood cells increase in every case, the white blood cells fluctuate, the

blood picture of Arneth-Schilling is changing to the right, the neutrophils are decreased, and the eosinophils, monocytes and lymphocytes are increased. This all means a change in the blood picture which seems to be the most favorable for the organism in its fight against tuberculous infection.

ZENTAY, St. Louis.

THE RELATION BETWEEN CATTLE AND HUMAN TUBERCULOSIS. ANDVORD, Norsk Mag. f. Lægevidensk. **86**:361, 1925.

The infection with bovine tubercle bacilli comes from milk and its products. This infection is most frequently found in early childhood (up to the fifth year), usually as a primary infection of the lymphatic glands of the neck and of the abdominal organs. During later childhood (from 5 to 15 years) the bovine infection is met in the more secondary forms, as a part of scrofulotuberculosis. In adults, the bovine infection seems to play only an inferior rôle. The author then discusses the question whether or not such a slight bovine infection of the lymphatic glands, originating from a benign cattle tuberculosis has, when healed, any effect on the child's organism as to the future susceptibility to the more severe infection from human lung tuberculosis.

The author is of the opinion that a benign bovine infection in childhood may be looked on as immunization against the severe human infection in adult life. He mentions that an antagonism usually is found in different regions of the world between the frequency of benign cattle tuberculosis and the mortality of human lung tuberculosis. England, Scotland and Denmark, for instance, have a relatively low mortality from phthisis, whereas the mortality in Norway and Sweden is high. The frequency of cattle tuberculosis is reversed in these countries, much cattle tuberculosis in England, Scotland and Denmark, not so much in Norway and Sweden.

TOVERUD, Oslo, Norway.

TREATMENT OF LUNG PHTHISIS WITH SANOCRYSIN. KNUD FABER, Ugesk. f. Laeger., 1925, p. 315.

The author reports a series of thirty-three persons afflicted with the ordinary forms of lung tuberculosis, who are being treated with "Sanocrysin." Briefly, the facts may be summarized as follows: twelve patients are still in the beginning stages of the treatment, three have discontinued it, two have died and sixteen have practically completed the treatment. Four of the last group are described in detail. In these four, the marked improvement is, according to the author, due to "Sanocrysin," as the prevalent treatment at a sanitarium would have required six months to accomplish what "Sanocrysin" did in from six to eight weeks.

Special emphasis is placed on the dangers attending this treatment, such as shock, high fever which may last for a long time, and albuminuria which prevents rapid progress of the treatment. When albuminuria makes its appearance the patient is also suffering from dyspnea, nausea, vomiting and anorexia. These symptoms initiate the marked loss of weight which occurs almost uniformly.

The use of serum to combat the albuminuria has not proved successful. If albuminuria has persisted for two days, the serum injections appear to be

of no value, and if the injections are continued, the albuminuria appears to persist longer.

The most persistent and the highest temperatures have been noted in patients having the least lung involvement, and in these, the severity of the reaction increases with the number of injections, indicating that the toxicity of "Sanocrysin" is directly responsible.

While "Sanocrysin" is no wonder remedy for tuberculosis as viewed from the present findings, the author thinks it deserves a fair trial over a period of years, as the results obtained are impressive and no remedy so far given a trial is comparable with "Sanocrysin."

SCHLUTZ, Minneapolis.

Internal Diseases

THE INFLUENCE OF THE GALLBLADDER ON INTESTINAL MOTILITY. BENJAMIN M. BERNSTEIN, Am. J. M. Sc. **169**:838, 1925.

To test the influence of the gallbladder on the intestinal motility, bile and various extracts of gallbladder mucosa were fed to normal and cholecystectomized dogs. The feeding of gallbladder bile produced a restoration of the motility to normal in the cholecystectomized animals, and an increased motility in the normal dog. Bile salts in fairly large doses, and aqueous and alcoholic extracts of the gallbladder mucosa were ineffective. An ether extract of the gallbladder mucosa, however, restored the disturbed motility in the cholecystectomized dogs and increased that in the normal dog. Cholesterin given alone restores the motility in the dogs on which an operation was performed, but has no effect in the normal dogs, while if given with the ether extract it produces no effect in the animals which were operated on, but the combination does increase the motility of the normal animal.

From these results the author concludes that the substance secreted by the gallbladder is hormonal in character, that it has a regulatory effect on the intestinal motility, and suggests that its absence produces an imbalance in the normal action of the circular and longitudinal muscle fibers of the intestinal tract.

EXPERIMENTAL STUDIES ON THE COLOR OF THE BILE FROM THE GALLBLADDER AND LIVER. A. WINKELSTEIN and P. W. ASCHNER, Am. J. M. Sc. **169**:842, 1925.

By means of suitably arranged cannulas, it was possible to observe the appearance of bile from the common duct, the hepatic duct and the duodenum, separately. The observations were made with the gallbladder in situ and also after its excision. Results indicate that the gallbladder is the source of the dark bile; that coming directly from the liver is always yellow, but that collected from the common duct of the fasting animal is quite dark, ranging from tarry or deep greenish brown to a dark brown; after cholecystectomy the same animal exhibits only yellow bile in the common duct. Observation on the duodenal contents show that their color inclines to imitate the appearance of the bile in the common duct, though not closely.

Installation of 25 per cent. magnesium sulphate solution into the duodenum was followed by no change in the color of the bile from the common duct, whether before or after excision of the gallbladder.

PARSONS, Ann Arbor, Mich.

RECURRENT VOMITING IN ITS RELATIONS TO ABNORMALITIES OF THE GASTRO-INTESTINAL TRACT. CHARLES GILMORE KERLEY, N. Y. State J. Med. **25**: 301, 1925.

Roentgen-ray study of 147 cases of persistent digestive disorders in children has led to the conclusion that systemic intoxication of intestinal origin is operative in the causation of recurrent vomiting. Delayed emptying of the stomach or intestine is often found associated with ptosis of the stomach or cecum, V-shaped transverse colon, elongated and sacculated sigmoid or spastic sphincter ani.

Management comprises abdominal support, a diet consisting largely of fruit, vegetables and cereals, massage, and adequate elimination. The results have been usually satisfactory.

GRAVES, New York.

OBSERVATIONS ON THE TREATMENT OF ACUTE CYCLIC VOMITING OF CHILDHOOD WITH GLUCOSE SOLUTION AND INSULIN. DAVID GREER, South. M. J. **18**:395, 1925.

The author treated two patients with severe cyclic vomiting with glucose solution and insulin. Five per cent. glucose solution given alone by hypodermoclysis or proctoclysis gave no relief. Prompt relief was obtained in one case by the additional use of 10 units of insulin and in the second case by the use of 15 units given in two separate doses of 10 and 5 units each.

SCHLUTZ, Minneapolis.

A CONTRIBUTION TO THE STUDY OF ACUTE LEUKEMIAS. PIERO BRUSA, Clin. Pediat. **7**:193-222, 1925.

The marked increase in the number of white blood cells, both the mature and immature forms, is often the terminal expression of the leukemic process.

Acute leukemias are of great importance to the pediatrician, but they often pass unnoticed at this early stage.

The author reported a case occurring in a boy, aged 11 years. The patient presented a marked cervical adenopathy. A clinical diagnosis of tuberculosis was made. Biopsy was done and on histologic examination, the gland showed numerous immature white cells; some of the leukocytes contained a basophilic lipoid granular material. Many of the leukocytes in the blood stream presented similar characteristics. The total white count at this time was 9,999.

The adenopathy was interpreted as an acute manifestation of a pre-existing leukemia.

ZAMBARANO, Washington, D. C.

TWO CASES OF MEDIASTINAL TUMOR. LUIS MORQUIO and ALEJANDRO VOLPE, Arch. españ. de pediat. **9**:193, 1925.

The authors report two cases of mediastinal tumor, both histologically similar but formed or derived from different parts of tissue. In the one case the tumor was apparently formed at the expense of the mediastinal glands; in the other, it seemed to be formed at the expense of the thymus.

Both tumors were of the type of lymphocytomas. The tumor which developed from the mediastinal glands extended laterally into the pleural cavity and during its early development caused little dysfunction or embarrassment. In the second case the tumor developed in the anterior mediastinum, causing early compression of the trachea and the large vessels and resulting embarrassment and grave dysfunction.

On account of a persistent fever in the first case, a generalized bacillosis was thought of. Tuberculosis and leukemia were also considered. A biopsy of an enlarged supraclavicular gland revealed the true nature of the condition, indicating the probable presence of a lymphosarcoma. The roentgenogram finally demonstrated the presence of the tumor.

In the second case, on account of the anterior location of the tumor mass, the symptoms rapidly became pronounced. The roentgenogram revealed the tumor early and the diagnosis was comparatively easy.

Both tumors were inoperable and roentgen-ray treatment failed to palliate or give relief.

SCHLUTZ, Minneapolis.

GAUCHER'S DISEASE. LUDWIG PICK, Med. Klin. **20**:1812, 1924.

The large, clear Gaucher cells arise from the reticular histiocytes of the spleen and lymph glands. They apparently arise also in the bone marrow. The cells also arise from clasmatocytes in Glisson's capsule of the liver, in the adventitia, peri-adventitia of the central veins of the lobules, and also from the adventitia cells of the arterioles in the spleen. Gaucher's disease is a congenital, familial, constitutional, specific disturbance of the metabolism and belongs to the group of congenital metabolic anomalies with Niemann's lipoid cell splenohepatomegaly, alkaptonuria and cystinuria. The nature of this metabolic disturbance depends on the chemical nature of the Gaucher substance in the specific cells.

PETERMAN, Rochester, Minn.

EMPHYSEMATOUS BRONCHITIS OF INFANCY AND CHILDHOOD. KURT EHLE, Monatschr. f. Kinderh. **30**:17, 1925.

The writer describes a number of cases called by Heubner "asthmatic bronchitis" and by Finkelstein "spastic bronchitis." In the Gottingen Clinic, the term "emphysematous bronchitis" has been applied because the striking finding is the emphysema.

The primary symptom is restlessness. Following this comes dyspnea with possibly cyanosis. Respiration becomes noisy and the picture may be severe enough to simulate a diphtheritic stenosis. A point of value, however, is that the stridor is expiratory and not inspiratory. The facial expression denotes anxiety. The head is retracted and the back arched. The thorax is fixed in position of deepest inspiration. The picture is almost that of meningitis. Percussion and auscultation show scattered patches of dulness in a markedly emphysematous chest, with various bronchitic and asthmatic râles. The roentgen ray shows little of value.

The picture is almost identical to the bronchotetany of Lederer, but electrical reactions rule out this possibility.

In spite of the theories offered as to etiology, one can say no more than that the disease seems to occur in children of a neuropathic constitution. The treatment is atropin sulphate by mouth in doses of at least 0.5 mg., three to four times daily. The writer has not had much success with this. Epinephrin in doses of 0.2 to 0.5 c.c. seems without effect. The most successful treatment is urethane. It seems to act by paralyzing the vagus endings and as a narcotic. The doses given are larger than customary. A child, aged 3 months, may get by mouth from 0.3 to 0.5 gm.; aged 6 months, from 0.6 to 1 gm., and aged 2 years, 1.5 gm. Bromids are also of value. A child, aged 1 year, may have from 1.5 to 2 gm. daily. In addition, children should be protected from any excitement or unnecessary manipulation.

Eighty cases are described.

EXPERIENCES WITH INSULIN IN JUVENILE DIABETES. R. FREISE, Monatschr. f. Kinderh. **30**:73, 1925.

The writer discusses in a general way the results in the treatment of six cases of juvenile diabetes with insulin. He is particularly enthusiastic about it in diabetic coma.

For the average case he uses it in dosage of 0.3 to 0.5 units for every gram of sugar excretion.

He agrees with American observers that the action becomes apparent about one hour after the injection and lasts from six to seven hours.

The results of the therapy are brilliant not only because lives are saved and that sugar tolerance is increased but also because the children are in such good condition and so contented during the treatment.

In one case an overdose threw a patient into a state of coma which persisted until sugar was given. Twenty cubic centimeters of a 4.5 per cent. sugar solution resulted in recovery in two minutes.

GERSTLEY, Chicago.

MILIARY NECROSIS OF LIVER IN INFANTS. L. SCHWARTZ, Virchows Arch. f. Path. Anat. **254**:203, 1925.

Schwartz studied three instances of liver necrosis which he observed at necropsy during a period of eight months. The study proposes to show that it is erroneous to refer to them as pseudotuberculosis. This name had been used because of their resemblance to similar lesions found in the lower animals. The changes in the reported specimens did not show the slightest resemblance microscopically or histologically to true tuberculosis. Bacteria from the patients were diphtheroid in type. Schwartz regards miliary necrosis as an entity, an infectious process having its origin in some birth incident, and manifesting itself in the first few days of life. Premature infants and twins seem particularly susceptible.

SCHWARZ, Milwaukee.

THE ETIOLOGY OF LYMPHOGRANULOMATOSIS. S. KAWATSUMA, Frankfurt. Ztschr. f. Path. **31**:450, 1925.

As cell inclusions have been considered a possible causal factor in Hodgkins' disease, the investigator has focused his attention on these, searching through at least 300 slides from each of a goodly number of collected cases of this condition. The preparations were stained by the Giemsa method and were examined on ruled stages so as to cover each one completely. In only four instances did Kawatsuma find any cell inclusions worthy of the name, and he explains all of them on the basis of nuclear degeneration. He concludes that neither spirochetes nor ray fungi are worthy of consideration and that now, as twenty-seven years ago, we must decide whether a connection between tuberculosis and lymphogranulomatosis may not be found to be the best solution of the question.

EXPERIMENTAL STUDIES ON THE ETIOLOGY OF LYMPHOGRANULOMA. A. GRUMBACH, Frankfurt. Ztschr. f. Path. **31**:530, 1925.

Grumbach has isolated an organism from six cases of Hodgkins' granuloma, during the stage of acute exacerbation. He describes its bacteriologic peculiarities in detail giving its cultural characteristics, morphology and tinctorial reactions. At first it is coccoid, but develops into a short, rod-shaped form,

with irregular staining, not unlike *B. diphtheriae*, but definitely different from Hoffmann's bacillus and the forms classes as "Pseudodiphtheriae." In time it develops club-shaped, irregular forms and, after a month or two, branching ones. The organism isolated from all six cases is morphologically constant and appears to be very closely related to the Klebs-Loeffler bacillus in its cultural and staining qualities.

This investigator has injected mice, rabbits, guinea-pigs and one monkey, with the organism. Irrespective of the method of inoculation employed, they all developed lesions as a consequence, after from four to six weeks. The characteristic lesion is a chronic interstitial pneumonitis typified by the production of large numbers of eosinophil leukocytes and large cells, with pale, vesicular nuclei. Cells resembling the Sternberg (Dorothy Reed) giant cell were also observed. The interstitial exudate causes a marked narrowing of the pulmonary alveoli and respiratory embarrassment. The regional lymph nodes become involved early, and the peribronchial connective tissue may undergo considerable thickening. The lesions are histologically quite similar to those of Hodgkins' granuloma, and Grumbach concludes that the interstitial changes in the lung are due to involvement of the interalveolar lymphoid tissue. He admits that his experimental lesions differ in their primary site from those seen in human beings, and modestly makes no claim as to having solved the problem, merely asking that his suggestive work be tried out in other laboratories and reported on.

Foot, Cincinnati.

Extensive Diaphaneity in Slightly Macrocephalic Skulls and Some Data on the Knowledge of Hydromacrocephaly. J. Bokay, Orvosi hetil. **69**:145, 1925.

In cases of slight macrocephaly, where one would not suspect the presence of any hydrocephalus, the transparency examination after Strassburger will often reveal an internal hydrocephalus.

The author has observed nine cases of microcephaly in which the transparency showed a definite internal hydrocephalus.

Experimental Studies on the Pharmacological Effects of Insulin. G. Hetenyi, Orvosi hetil. **69**:328, 1925.

In animal experiments the sugar content of the blood and the tissues was determined in different stages after administration of insulin.

The first change found was a decrease of blood and tissue sugar with unchanged sugar content of the liver.

In the next stage, the sugar in the liver begins to decrease.

In the so-called hypoglycemic stage, the following syndrome can be observed in the sugar content of the organs: blood and tissue sugar is further decreasing, sugar content of the liver begins to increase.

Epinephrin injection will stop these changes. At the same time the comatose stage of the animal is relieved.

New Dietetic Treatment of Graves' Disease. R. Balint, Orvosi hetil. **69**:349, 1925.

Tryptophan being the main component of thyroxin, the author tried a diet with proteins of a low content of tryptophan. These proteins are found in corn, rye, potatoes, green vegetables and fruits.

The results seen in a few cases seem to be encouraging.

INSULIN AND GASTRIC SECRETION. L. DETRE and R. SIVO, Orvosi hetil. **69**:399, 1925.

Insulin administered for several days had a stimulating effect on the gastric secretion.

Single insulin dose causes an increase of acid concentration in the majority of cases, while in the other cases no change can be seen.

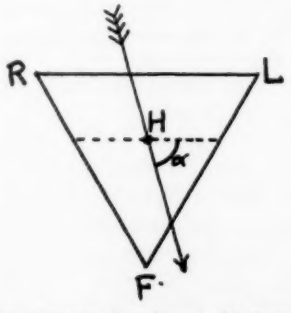
ZENTAY, St. Louis.

ELECTROCARDIOGRAPHIC OBSERVATIONS ON DEXTROCARDIA. E. GORTER, Acta Pediat. **4**:125 (April) 1925.

Most observers have found that when dextrocardia occurs alone, the electrocardiogram is quite normal, but in cases of complete situs transversus the "electrical axis of the heart" is altered (that is, Lead 1 shows complete inversion of the normal electrocardiogram with negative P, R and T waves, while Leads 2 and 3 are interchanged). Gorter's experience in five cases of dextrocardia does not confirm this entirely. In his only case of complete transposition of the viscera there was an inversion of the electrocardiogram, but of the four cases with dextrocardia alone, only three had a normal electrical axis, while the fourth showed the typical inversion changes.

THE DETERMINATION OF THE ELECTRICAL AXIS OF THE HEART. W. EINTHOVEN, Acta Pediat. **4**:136 (April) 1925.

The electrical axis of the heart, indicated by the arrow in the diagram, can be determined accurately by means of a special electrocardiographic apparatus which records the three leads simultaneously. The angle α which



The electrical axis of the heart.

this axis forms with the horizontal plane is normally from 60 to 80 degrees. In typical inversion of the heart, the angle varies between 97 and 180 degrees. Measurements of this angle are given for the five cases of dextrocardia reported by Gorter (previous paper).

HOLT, Baltimore.

Nervous Diseases

THE PATHOGENESIS OF ADIPOSOGENITALIS DYSTROPHIA. E. J. KRAUS, Med. Klin. **20**:1328, 1924.

Kraus cites three additional cases of tumor in the midbrain, affecting the hypophysis and producing dystrophia adiposogenitalis. He is of the

opinion that there is in these cases a disturbance of the carbohydrate metabolism, which allows the excessive deposits of fat. Atrophy of the pancreas was usually found. Kraus agrees with the theory that the disease is a condition of the anterior-pituitary stalk — midbrain system. The absence of obesity in acromegaly may be due to a disturbance of the carbohydrate metabolism caused by the eosinophilic adenoma.

PETERMAN, Rochester, Minn.

EXPLANATION OF THE TROUSSEAU PHENOMENON. OTTO TEZNER, Monatschr. f. Kinderh. **29**:728, 1925.

Tezner finds that the results obtained in previous experiments were possibly inaccurate, owing to a faulty technic. In the meantime, until he can repeat the work, the question whether the Trousseau phenomenon is due to anemia or not must remain unanswered.

SIGNIFICANCE OF THE COLLOID REACTION OF CEREBROSPINAL FLUID FOR THE DIAGNOSIS OF NERVE DISEASES IN CHILDHOOD. ALFRED MARCHIONINI, Monatschr. f. Kinderh. **30**:1, 1925.

One of the advances in our knowledge of cerebrospinal fluid has been the study of its colloidal reactions, particularly with reference to gold chlorid. This test has proved of considerable value, but has also offered a number of difficulties to investigators. To overcome these difficulties, various substitutes have been suggested, among them, mastixhydrosol, which was suggested by Emanuel in 1916. Since then, various modifications of the technic have been suggested.

The writer has examined eighty spinal fluids with the latest modifications of this test, and finds it of definite value. The reactions permit three definite types of curve: a normal, a syphilitic and a meningitic curve. The writer believes that this test is more delicate than the Wassermann test in spinal fluid.

GERSTLEY, Chicago.

ACUTE ASEPTIC MENINGITIS: A NEW INFECTIOUS DISEASE? ARVID WALLGREN, Acta Pediat. **4**:158 (April) 1925.

Under this heading the author describes cases of meningitis characterized by (*a*) sudden onset with frank meningeal symptoms, (*b*) sterile spinal fluid with mononuclear reaction, and (*c*) rapid recovery without complications. Such cases are often considered to be either atypical poliomyelitis or atypical epidemic encephalitis. Since no constant relation exists between the occurrence of these cases and the prevalence of epidemic encephalitis or poliomyelitis, the author feels that the condition is a distinct entity.

DIFFICULTY IN CHEWING AND SWALLOWING OF FAMILIAL OCCURRENCE. ALFHILD TAMM, Acta Pediat. **4**:194 (April) 1925.

The author describes the case of a child, aged 4 years, who was unable to chew or swallow properly. The difficulty had existed almost from birth. By a laborious system of training, the child was eventually taught to chew and swallow almost normally. There was a family history of similar disturbances, but not in the child's immediate family. Although there was evidence of a neurotic element in this disorder, the author believes that this factor will not account for it entirely. He considers that there is an organic lesion — a failure of development of the centers which control these functions.

HOLT, Baltimore.

Diseases of the Eye

A Contribution to the Etiology of Experimental Keratomalacia. G. Marshall Findlay, Brit. J. Exper. Path. **6**:16, 1925.

Keratomalacia has been produced in many experimental animals by dietary deficiencies or disproportions affecting both the vitamin and the salt factors. The exact pathogenesis of the underlying metabolic defect is unknown. Keratomalacia, as an isolated expression of the general disturbance, has been shown to be accompanied in both animals and man by pathologic changes in the para-ocular glands. These anatomic changes seriously affect the function of the glands as evidenced by the brief period of lacrimation coincident with the onset of the keratomalacia, this hyperfunction being followed quickly by a markedly decreased output of tears which become serosanguineous in character. In animals on a diet free from vitamin A, the onset of the eye changes can be hastened by the repeated administration of pilocarpin, which at first causes lacrimation but which is soon followed by a decrease in secretion of tears and rapidly developing keratomalacia.

Attempts to isolate from the conjunctival sacs of affected animals microorganisms which would produce the same changes when transplanted to the eyes of normally fed animals, or hasten the appearance of keratomalacia in animals on deficient vitamin A diets, have all been unsuccessful.

Fleming, in 1922, showed that human tears contain a substance — lysozyme — having a powerful lytic action on certain bacteria. Rabbits on normal diets possess a similar substance. During the onset of keratomalacia in rabbits on a diet free from vitamin A, this lysozyme decreased. On the basis of this finding, an attempt was made to prevent the onset of eye changes in rats, kept for twenty-five days on a diet producing keratomalacia, by irrigating their conjunctival sacs twice daily with normal undiluted human tears. During the succeeding twenty-five days, only one out of ten rats thus treated developed the typical eye changes, whereas eight out of ten animals whose conjunctival sacs were washed twice daily with physiologic sodium chlorid solution developed the usual keratomalacia. Locke's solution used in the same way showed more protective power than the physiologic sodium chlorid solution but was not so effective as human tears.

The author does not believe that the decrease of lysozyme is the only underlying cause of the condition called keratomalacia. The fact that this lytic substance is decreased in the tears of rabbits in the active stage of this condition, and that its use in the form of irrigations of human tears sharply decreases the incidence of eye changes in rats with potential keratomalacia, leads to the conclusion that it has some rôle in the development of the local eye changes of the metabolic disease usually designated as keratomalacia.

On the Specificity of the Protein of Human Tears. Alexander Fleming and V. D. Allison, Brit. J. Exper. Path. **6**:87, 1925.

Human tears contain proteins of the general chemical nature of albumin and globulin. It was shown by the use of rabbit antitear serum titrations that these proteins are common to all samples of human tears, but differ from the proteins in animal tears, and also from those occurring in human blood serum, tissues and secretions. These findings are in accord with the study of Hektoen on the specificity of the protein in semen.

Hoag, New York.

Diseases of the Nose and Throat

CARCINOMA OF THE NASOPHARYNX IN EARLY CHILDHOOD. H. ROSENBUSCH, Frankfurt. Ztschr. f. Path. **31**:507, 1925.

This is the report of a case of "carcinoma solidum simplex" of the nasopharynx in a child, aged 1¼ years, with extension into the cranium and metastasis to both suprarenals and the cervical lymph nodes. The condition developed ten days after a fall from a "kiddie car," which may have hurried its progress, but scarcely served as an etiologic factor, according to the writer. He discusses the literature on similar tumors and speculates as to the origin of this one. He does not believe that it arose from Radke's pouch, or from the hypophysis, for it does not correspond histologically with such tumors. He claims that this is not only the youngest case of carcinoma of the pharynx, but also the youngest case of carcinoma of any region whatsoever to have been recorded.

FOOT, Cincinnati.

Diseases of the Skin

PROTEIN SENSITIZATION IN PRURITUS WITH LICHENIFICATION. FRED WISE and MAXIMILIAN A. RAMIREZ, Arch. Dermat. & Syph. **11**:751 (June) 1925.

Pruritus with lichenification is a well defined clinical entity occurring at all ages. It is considered by some a form of eczema though it differs from eczema both clinically and microscopically. It is a neurodermitis. The primary form is more common in children. Various views as to etiology have been held. Because of the association with asthma and hay-fever in some of the authors' cases, they investigated protein sensitization. Ten cases are reported in which the patient was sensitive to some protein and in which relief was obtained by elimination of the offending protein or desensitization.

MONILIA AS A POSSIBLE ETIOLOGIC FACTOR IN PSORIASIS. MOYER S. FLEISHER and M. WACHOWIAK, Arch. Dermat. & Syph. **11**:756 (June) 1925.

In thirty cases of psoriasis, monilia were found in the feces in 82 per cent., in the blood in 21 per cent. and in skin scrapings in 46 per cent. This is in marked contrast to the almost negative findings in normal cases. Vaccines prepared from the organisms found were of value in treatment. It is believed that these organisms are a factor in the etiology of psoriasis.

JEANS, Iowa City.

VIRUS OF HERPES. ITS IMMUNE REACTIONS AND ITS RELATION TO THAT OF ENCEPHALITIS LETHARGICA. J. R. PERDRAU, Brit. J. Exper. Path. **6**:41, 1925.

The author isolated from spontaneous and recurrent herpes labialis, types of virus which he designated as dermatropic and neurotropic, depending on their selective tissue action. The neurotropic virus produced encephalitis in rabbits quite routinely when injected intracerebrally and in about 70 per cent. of the cases when applied to the nasal mucosa. The author called attention to the fact that rabbits are subject to "spontaneous" encephalitis occurring in outbreaks suggestive of endemics, but he believes that the two forms can be distinguished by differences in the clinical course and the histologic changes in the nervous system. He believes that the results of this study were not influenced by spontaneously occurring encephalitis in the animals.

It is obvious that immunity against this neurotropic virus cannot be produced by intracerebral or intranasal inoculations because of its great virulence by these routes. Intradermal inoculation, however, produces a cerebral immunity which is fully established in eleven days and lasts about three months. This period cannot be prolonged by repeated intracerebral inoculations. Application of the virus to scarified skin may produce a cerebral immunity but occasionally it results in a fatal encephalitis, especially if the scratch is deep. The majority of animals which have had this temporary, and apparently local, cerebral immunity eventually succumb to intracerebral inoculations of the virus, and many show symptoms recalling those of encephalitis lethargica (epidemic encephalitis) in man, and the virus cannot be recovered from the brain. The histologic changes in the brains of these animals are identical with those obtained from inoculation of emulsions of brain from cases of encephalitis lethargica (epidemic encephalitis).

A Clinical and Experimental Study of a Case of Herpes of Finger. S. Nicolau and P. Poincloux, Ann. de l'Inst. Pasteur **38**:977, 1924.

A herpes of the forefinger was studied in its various recurrences during the last five years, and a virus was isolated during these local exacerbations. During two of these recurrences, the patient exhibited mild symptoms of central nervous system involvement and at such times the isolated virus showed greater neurotropic properties in animals than did the virus isolated from vesicles which were not accompanied by neurologic symptoms. The authors discuss the possibility of this virus being at a transitional stage between one causing herpes of the skin and one capable of producing encephalitis lethargica (epidemic encephalitis).

Hoag, New York.

Herpes Zoster and Varicella. A. Netter, Bull. et mém. Soc. méd. d. hôp. de Paris, 192, 1925.

In this communication, Netter adds further clinical evidence to that which he has formerly published, of the connection between herpes zoster and varicella, in brief reports of seven cases in which herpes zoster was followed in from thirteen to twenty-one days by varicella. He also reports that Urbain of the Pasteur Institute has succeeded in demonstrating the probable identity of the two diseases in several instances by complement fixation. The author states his belief that: "Herpes zoster is not merely a specific infectious disease. . . . It is more often, if not always, a manifestation of infection by varicella."

Josephs, Baltimore.

Experimental Inoculation of Herpes Zoster in Human Beings and the Relation of Herpes Zoster to Varicella. Karl Kundratitz, Monatschr. f. Kinderh. **29**:516, 1925.

Kundratitz was able to transmit herpes zoster from one child to another by inoculating the contents of the vesicles into the skin. In an occasional case the resulting reaction resembled varicella though usually the lesions remained localized. Those children who had already had varicella could not be inoculated. This is the first time that herpes zoster has been produced in this fashion, and is of particular interest in view of the prevailing theory that the disease is of nervous origin.

THE CLASSIFICATION AND TREATMENT OF ERYTHRODERMIA DESQUAMATIVA. H. KAUFMAN, Monatschr. f. Kinderh. **30**:64, 1925.

There has been considerable discussion whether the disease described by Leiner as erythrodermia desquamativa is a clinical entity or is simply a form of seborrheic eczema.

Kaufman believes it to be a clinical entity. In contrast to eczema, recurrences are rare and the skin does not respond readily to irritants. Also, there are no other symptoms suggestive of exudative diathesis.

The prognosis is not as grave as has been held, for in eighteen cases there was only one death.

The treatment consists of bland applications to the skin and the use of intramuscular injections of blood.

GERSTLEY, Chicago.

THE RELATION BETWEEN ERYTHEMA NODOSUM AND TUBERCULOSIS. HARALD BELFRAGE, Acta Pediat. **4**:183 (April) 1925.

The author comments on the recent literature indicating that erythema nodosum is of tuberculous rather than of rheumatic origin. He reports five cases in which the relation between this disease and tuberculosis seemed more than fortuitous. In three of these there was no evidence of tuberculosis some months prior to the attack of erythema, and the Pirquet test was negative. At the time of the attack of erythema, the Pirquet test was positive and roentgenographic evidence of mediastinal tuberculosis was found. The other two patients were known to have latent tuberculosis. This became active at the time of the attack of erythema.

HOLT, Baltimore.

Surgery and Orthopedics

NECROSIS OF THE UPPER JAW IN THE NEW-BORN AND NURSLING. M. PAUNZ, Ztschr. f. Hals-, Nasen-u. Ohrenh. **11**:49 (March 14) 1925.

The child suddenly becomes sick with high fever; one cheek is more or less inflamed and swollen; the inflammatory edema extends also to the upper and to the lower lid. Frequently, abscess formation can be demonstrated. Copious thick pus emanates from each nostril, the alveolar region is thickened and one or more suppurative and granulating fistulas can be noticed. The swelling may extend to the hard palate. Abscesses may be found in other parts of the body. Later the upper jaw becomes either partially or totally necrotic. In almost every case a cure results after sequestration of bone, and of some teeth buds. Schmiegelow called septicopyemia acute osteomyelitis of the upper jaw. Bourraqué, Canestro and Schlemmer assumed a primary suppuration of the antrum of Highmore. Hajek considers it to be a primary osteomyelitis of the upper jaw and a secondary suppuration of the antrum of Highmore. Logan Turner assumes the same. Seven cases in point have been observed in the University Children's Clinic in Budapest during the last years. Their ages were from 3 week to 3 months. In one case the beginning of the disease was noticed after birth, in the others when the children were 5 days, 8 days, 2 weeks, 6 weeks, 3 and 3½ months old respectively. In each child the face was swollen, and pus discharged from the nostrils. Three cardinal symptoms had been present: 1. Edema and frequently abscess formation in the face and eyelids. 2. Copious discharge from the respective nasal cavity. 3. Periosteal swelling of the alveolar process of the respective upper maxilla with

suppurative fistulas in which the probe touched rough bone and necrotic teeth buds. In the majority of cases, it was a local disease with more or less severe symptoms, but in three cases pyemic and septic general symptoms developed. It can be easily imagined, Paunz states, that the maxillary antrum, which has been infected by the nasal route, furnishes the origin of the osteomyelitis. In the cases which came to necropsy the suppuration of the antrum of Highmore, without the infection of the ethmoid cells, could be established without a doubt. The prognosis is favorable in the purely local, doubtful in the pyemic and unfavorable in the septic cases. The treatment is simple. The abscesses are opened, the fistula channels are enlarged and the necrotic bone and teeth buds are removed. Only necrotic pieces of bone and teethbuds which are ready to be cast off must be removed. This necessitates several operations. Paunz describes his seven patients, five of whom were cured.

AMBERG, Detroit.

FORMATION OF WEDGE VERTEBRAE IN CONGENITAL SCOLIOSIS. H. LEHMANN-FACIUS, Frankfurt. Ztschr. f. Path. **31**:489, 1925.

This paper is of interest in connection with its predecessor. The writer reviews the literature and discusses the various theories as to the etiology of supernumerary wedge-vertebrae, quoting extensively from Falk and giving an excellent bibliography. He states that the formation of seemingly supernumerary vertebrae may be referable to the misplacement of hemimetameric segments during that period when each vertebra has a paired primordium, with an oblique fusion of these half-segments. In other words: each vertebra has at this time two halves which should unite horizontally; if the right half of one vertebra unites obliquely with the left half of the one beneath it, and so on through several segments, one will have a portion of the spinal column in which all the vertebrae are obliquely fused. The left half of the upper vertebra will be left unpaired as will the right half of the lowermost, leaving two wedge-shaped, apparently supernumerary vertebral halves unfused. This leads to scoliosis.

FOOT, Cincinnati.

SPINA BIFIDA OCCULTA AS AN ETIOLOGIC FACTOR IN ORTHOPEDIC DISEASE. O. E. SCHULZ, Casop. lek. Cesk. **63**:1113, 1145, 1177, 1203 (July-Aug.) 1924.

The author reviews the literature since Virchow's description in 1875 of a case of spina bifida occulta with hypertrichosis. A great many anomalies of the new-born about the lumbosacral region are described in detail. A series of case reports is given with the peripheral symptoms and findings. Occult spina bifida is not a rare finding. At times no symptoms are produced throughout the life of the individual. In other instances, associated tumor masses of striated muscle, nerve tissue, glial embryonic cartilage and bone reticulum are found. Dural adhesions may produce atypical conus conditions with peripheral manifestations.

Enuresis nocturna was rarer in the female. In 50 per cent. of congenital pes varus, occult spina bifida was found. Other defects were claw-foot and club-foot. Secondary closure of some of the fissures was noted, but the residual tumors produced the orthopedic defects.

STULIK, Chicago.

SOME CONTRIBUTIONS TO THE ETIOLOGY AND PATHOGENESIS OF HERNIAS OF THE UMBILICAL CORD. A. KOOS, Magyar Orvosi Arch. **21**:54, 1924.

The author reports on two cases of hernias of the umbilical cord, neither of which can be explained by the theories of Ahlfeld, Aschoff and Kermauer

on the etiology of these hernias. These two hernias were caused respectively by an entosite and one by a so-called parasite. Radical operation by Lindfors' method, performed immediately after birth, is recommended as the best method.

ZENTAY, St. Louis.

RENAL TUMORS IN CHILDREN. J. C. SHIPPERS, Acta Pediat. **4**:141 (April) 1925.

The author describes twelve cases of malignant neoplasms of the kidney in children, aged from 1½ to 5 years. The tumors were either sarcomas or mixed embryonic tumors.

The usual symptoms were those of general malaise with a gradually enlarging mass in the abdomen. In only three cases was hematuria a striking symptom. Several of these patients were operated on, but none successfully. The author emphasizes the bad prognosis of this condition, and feels that an earlier diagnosis could often be made if the kidneys were carefully examined in all children. The results of therapy should then be much better.

HOLT, Baltimore.

Miscellaneous

THE HYPOTONIC CHILD. DONALD PATTERSON, Brit. M. J. **1**:301, 1925.

The author describes this type of child with the following symptoms: tiredness, lack of energy, indefinite pains, flat-feet, pallor, lack of appetite and general debility. Examination of these patients depicts the typically malnourished child of America producing the usual fatigue stance. The etiology is discussed under the following headings:

1. Confinement and lack of exercise.
2. Toxic theory of Vining.
3. Constitutional defect of Czerny (exudative diathesis), and finally concludes by suggesting that factors which tend to depress metabolism produce flabbiness, while factors which tend to stimulate metabolism cure flabbiness. Among the former might be considered confinement, lack of exercise, fresh air and sunshine; overclothing with consequent heat retention; overfeeding in relation to the child's energy output and especially overfeeding with a diet high in carbohydrate and low in animal fat, protein and vitamins. Among the latter are the reduction of the diet especially in cereals, administration of cod liver oil, sunshine, fresh air, exercise and massage.

BROWN, Toronto.

PROCEEDINGS OF THE ITALIAN PEDIATRIC SOCIETY. Clin. Pediat. **2**:120-125, 1925.

The Ombredanne Operation in the Treatment of Retained Testicle.—Camera, after reviewing the indications for operation and the various methods used in the treatment of undescended testicle, finally declared that the operation of Ombredanne (trans-scrotal orchidopexy) was the most successful. He cited a case of bilateral cryptorchidism in which both testicles were situated in the middle of the inguinal canals. The Ombredanne operation was attempted on one side and was successful. Three months after operation the testicle was in the scrotal sac and had doubled its original size. A similar operation is to be done on the other side.

Examination of the Spinal Fluid in Tuberculous Meningitis.—Spinal fluid findings in the various types of meningitis were carefully outlined by Fornara, and in reference to the diagnosis of tuberculous meningitis he concluded that

all clinical and laboratory data should be cautiously evaluated and, in the absence of the tubercle bacilli in the spinal fluid, the diagnosis should be very prudently made.

The Schick Reaction and Active Immunization.—The results obtained by Mensi and Segagni in over 100 infants after specific and nonspecific injections in those showing a positive Schick test, prompted the authors to conclude that it is possible for the positive reaction to change to negative after the injection of specific and nonspecific serums; they deduced from this that the reaction obtained was not due to the injected serum but to an immunity produced by the first toxin reaction. The toxins producing antibodies reserved their power again to stimulate antibody formation under a new nonspecific stimulus.

A Contribution to Pneumotherapy in Infantile Pulmonary Tuberculosis.—Bosco reported a case of tuberculous broncho-alveolitis involving the left upper lobe in a child, aged 12 years. Because of severe attacks of hemoptysis, artificial pneumothorax was done. Marked clinical improvement followed the procedure. The roentgen ray demonstrated however, that, although compression of the lung was successful, there was a notable displacement of the mediastinum and a flattening of the diaphragmatic dome. These complications prevented a further increase in the endopleural pressure and it was therefore impossible to break up a few small apical adhesions and to compress the lower portion of the lung completely. Therefore, with even a partial pneumothorax, progress of the case was most satisfactory. He further remarked that he believed compression therapy was more efficacious in infants than in adults because of the greater succulency and more liberal yielding powers of the infant tissues.

The Syndrome of Macrogenitosoma-Precox.—Merlini presented a girl, aged 6 years, who weighed 38 kg., with exaggerated body development and marked secondary sexual characteristics (adult mammary development, adult distribution of hair, precocious development of the external genitalia). She also had regular menstrual periods, with onset when she was aged 4 years. A few months previous to this she became totally blind. Roentgen examination of the long bones showed advanced ossification and complete closure of the diaphyso-epiphyseal junctions. Roentgenography of the skull confirmed the signs of increased intracranial pressure and a diagnosis of pineal tumor was made. There were no changes in the sella turcica.

Excluding the effects of the suprarenals, thyroid, hypophysis and other important endocrinous structures in the production of the condition, the author believes it to be a syndrome of pineal origin.

The condition is seen more in males in a ratio of 6:2. It is characterized by: (1) Precocious development of external genitals; (2) body development from five to ten years in advance of the normal for the actual age; (3) marked tendency to early and complete ossification of skeleton; (4) presence of secondary sex characteristics; (5) an intelligence proportionately below that of the age of the patient. Very frequently there are the signs of brain tumor added to these. There is no treatment; medical and surgical measures fail. The diagnosis is easy, and cannot be confused with infantile gigantism or pituitary infantilism.

Laryngeal Type of Tuberculous Meningitis.—Mensi reported a case of tuberculous meningitis ushered in by symptoms of laryngeal stenosis. The diagnosis of tuberculous meningitis was later specifically established by clinical findings and again confirmed at necropsy.

ZAMBARANO, Washington, D. C.

Society Transactions

NEW ENGLAND PEDIATRIC SOCIETY

Boston, Mass., May 8, 1925

KENNETH D. BLACKFAN, M.D., *Presiding*

THE DICK TEST AND SCARLET FEVER ANTITOXIN. Presented by DR. EDWIN H. PLACE.

This paper gave the results of work done with these products by Dr. Place and Dr. Adrian Boucart at the South Department of the Boston City Hospital. The Dick test he considered a reliable method of determining susceptibility or immunity to scarlet fever. The Dick test becomes negative at varying lengths of time after an attack of scarlet fever, and almost immediately after the injection of antitoxin. Dick toxin produces a transitory rash with symptoms resembling those of scarlet fever, and immunity, as registered by the Dick test, develops within a very few weeks or days. Antitoxin, developed by the Dicks' method of immunizing the horse with toxin, speedily cures the symptoms of scarlet fever, although it is no more efficacious than convalescent serum.

BIOLOGIC PRODUCTS AND SCARLET FEVER. Presented by DR. BENJAMIN WHITE.

The Dick test has not been as satisfactory as originally claimed and confusing results have been obtained with it. Active immunization produced by Dick toxin has frequently been found to be of short duration only. The Hygienic Laboratory in Washington has refused to license and standardize these products as yet. Dochez's method of immunizing horses for the production of antitoxin, by inoculating living cultures into an agar implantation is at least as satisfactory as the Dick method, and has been adopted by the Massachusetts antitoxin and vaccine laboratory. A limited amount of antitoxin is now available, and within a few months sufficient will be available for general distribution.

DISCUSSION

DR. RICHARD M. SMITH: I should like to ask Dr. Place what procedure he would recommend, either in a community, in a school or in a hospital if a case of scarlet fever occurred. Does he feel at the present time that all exposed individuals should be given the Dick test? What should be done with those who have a positive reaction to the Dick test?

DR. MORSE: I should like to know whether Dochez's serum has been used in active immunization as well as the Dicks' serum.

DR. LEWIS W. HILL: How reliable is the immunization with antitoxin? How soon does it come on after the injection and how long does it last? I want to ask Dr. White what is the method of preparing concentrated serum?

DR. PLACE: It is a little difficult to answer Dr. Smith's question. In the past, in the face of an epidemic of scarlet fever we were compelled to use the quarantine measures. In other words, we only watched for subsequent

cases. Now the question comes up whether we ought to do something active. Should we go ahead and culture that group and see how many are harboring the scarlet fever streptococci and immunize those persons afflicted? I think we should give antitoxin to those ill with scarlet fever, apply the Dick test to all exposed persons, immunize the positive cases and then wait and see what happens. We have strong evidence that the antitoxin serum is a protection against scarlet fever.

If the school really wants to do something more than the old practice of watching, a Dick test can be done and then immunize the positives. The important fact, however, is to find the source of the infection. A person may be infectious for long periods of time.

I think I feel a little more optimistic about this whole subject of scarlet fever than Dr. White does, and I think all we can do is to continue what we are doing and record our observations.

As regards to Dr. Morse's question as to whether we used Dochez serum as well as Dicks' serum, we have used both and have obtained the same results.

In regard to Dr. Hill's question, the immunity as shown by the Dick test has proved to be from five to eighteen weeks. We do not know how long it lasts.

As to whether the immunization with antitoxin in scarlet fever cases is reliable, I think it is. I think we have a great deal more work to do on this before we can come forward and say that this or that fact is absolutely so.

We cannot say for sure that the Dick test is a measure of immunity. To be absolutely sure of this fact we would have to observe the persons who had been tested for a long period of time. Of course, the ideal procedure would be to get large numbers of people, use the Dick test on them, and inject scarlet fever serum into those who were positive and watch them for a long period of time, as the Dicks did in some instances. In that way we would soon find out whether the Dick test was a real measure of immunity or not. I think it is going to be interesting to watch the nurses immunized with scarlet fever serum and see if they come down with the disease. If at the end of ten years these nurses, who were injected with scarlet fever serum, do not become ill with the disease, this observation will be of some value.

There is a great variation in the reaction in different individuals. In looking over the records of those who have had the Dick test, it is interesting to note how the mild cases remain mild and the severe cases remain severe.

In regard to Dr. Hill's question as to how the scarlet fever antitoxin is concentrated, I would say that the method used is the same as that used for the concentration of diphtheria antitoxin — that is, by salting out the pseudoglobulin and freeing it from fibrinogen, euglobulin and albumin through ammonium sulphate precipitation.

Dr. F. P. Denny: I have been very much interested in these two papers this evening. It is encouraging to know that the antitoxin is so effective, and even if the active immunization with the toxin does not work out, it seems to me a tremendous gain will be made with the use of antitoxin. As compared with diphtheria, scarlet fever is much less severe as regards fatality. I think there are about one-third as many deaths in the state from scarlet fever as there are from diphtheria, and if that one-third can be much reduced by the use of antitoxin this is most encouraging. We are not going to see so many neglected cases of scarlet fever as we see of diphtheria. The severe cases of scarlet fever are usually seen promptly and can be given antitoxin.

ST. LOUIS PEDIATRIC SOCIETY

May, 14, 1925

GEORGE M. TUTTLE, M.D., *President*

The meeting was held at the Missouri School for the Blind. Mr. Samuel McKnight Green, director of the school, and a number of the teachers, gave a demonstration of the methods used at the school. On concluding the program, the following paper was presented.

INFLUENCE OF PEDIATRICS ON OCULAR PATHOLOGY AS SEEN AT MISSOURI SCHOOL FOR THE BLIND. Presented by DR. H. D. LAMB.

Congenital syphilis is the most important single factor causing blindness in children. Among 507 recent pupils, of whom we have records of the ocular condition, congenital syphilis accounts for about 75 per cent. of optic atrophy (seventy-two cases), probably 30 per cent. of the uveitis (twenty-three cases), 80 per cent. of the chorioretinitis (twelve cases), and all the parenchymatous or interstitial keratitis (seven cases). In addition, there is reliable clinical evidence that it has probably been the etiologic element in some of the ocular maldevelopment and undevelopment. Out of 256 youthful blind persons who had blood Wassermann tests made, only nineteen were positive and two gave ++.

From the case histories, we find that meningitis has caused some optic atrophy, uveitis and corneal ulceration. Measles was the most important single element in causing corneal ulceration. Each of the acute infectious diseases has apparently been the etiologic factor in causing blindness in the form of corneal ulceration and uveitis; typhoid and scarlet fever may have accounted for optic atrophy in a few cases.

Book Review

THE HEALTH-CARE OF THE BABY. By LOUIS FISCHER, M.D. New York: Funk & Wagnalls Company.

This so-called handbook for mothers, nurses and physicians, "in its 15th edition, completely revised," is so full of inaccuracies and misstatements, gives so little usuable information for mothers, nurses, or physicians, and is so definitely below the standard set by other books of this type that it cannot be recommended.

News and Comment

INFANT MORTALITY

We are in receipt of the statistical report of Infant Mortality for 1924. This report is on the infant mortality of 667 cities.

It is most interesting to note that in 629 cities in the birth registration area in the year 1924, the death rate was 72.2, while in 1923 in the same area the death rate was 78. The number of cities reporting since 1919, that is, those having a birth registration, has increased from 520 to 667, which represents 95 per cent. of cities in this country, the total being 701. The lowest death rate came from New Philadelphia, Ohio, a city of 11,000 people, in which the death rate was but 25, as compared with 70 in 1920. Long Beach, Calif., leads the list of cities of 50,000 to 100,000 population with 41 and Seattle those of 250,000 or more, with 45. The highest rate was in Charleston, S. C., 153. Of the large cities, Pittsburgh led with 92.